Vol. 222 No. 3 SEPTEMBER, 1951 No. 953

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

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THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

SEPTEMBER, 1951

ORIGINAL ARTICLES

THE SYNERGISTIC ACTION OF PARA-AMINOBENZOIC ACID AND CORTISONE IN THE TREATMENT OF RHEUMATOID ARTHRITIS

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The beneficial effects of cortisone on rheumatoid arthritis are now well established[8,9,11]. Unfortunately these effects are not lasting and the majority of patients require continued administration of cortisone to insure continued relief. Since cortisone affects a number of metabolic processes[10] there have been undesirable side reactions[8,9,10] with the customary dosage schedules. Efforts have been made to produce relief from the symptoms of rheumatoid arthritis with smaller doses of cortisone and at the same time to reduce undesirable side actions and the high cost of treatment[5,6]. The search for synergistic agents to enhance the action of cortisone has so far been disappointing.

The authors became interested in the mechanism involved in the response of certain diseases of the collagen system to the administration of para-aminobenzoic acid which was established by Zarafonetis and his coworkers[13]. The metabolic effects of this substance have been studied extensively[2]. An impressive fact was that the known inactivation of estrogenic hormones by the liver[4,7,14] is inhibited by the addition of para-aminobenzoic acid[3]. The great similarity in structure of cortisone and the estrogens and the fact that the major portion of parenterally administered cortisone is inactivated in the body made it plausible to attempt to inhibit the destruction of cortisone by the simultaneous administration of para-aminobenzoic acid. Initial experiences with this method were encouraging[12]. The present report concerns the results obtained in the first 15 cases treated by this method for a significant period.

Method. For purposes of evaluation a controlled study was employed. Since the objective appraisal and grading of rheumatoid arthritis is fraught with pitfalls, each patient was used as his own control. All patients studied had moderately severe or severe rheumatoid arthritis which had previously proved refractory to other forms of treatment.

The 2 methods used for study were:

1. Patients were started on full dosage schedules of cortisone acetate until maximum relief of the symptoms of arthritis was obtained. This was usually for a period of 1 week. The daily intramuscular dose of cortisone was then reduced arbitrarily to 25 mg. On this dose all of our patients developed prompt relapse with severe subjective and objective symptoms and signs within a short time. When this relapse was established the sodium salt of para-aminobenzoic acid was given orally in doses of 1.5 gm. every 2 hours during the waking period for a total of 8 doses or 12 gm. per day in addition to the single daily intramuscular injection of 25 mg.

TABLE 1.—RESULTS IN 9 CASES OF RHEUMATOID ARTHRITIS TREATED BY METHOD 1 (CORTISONE ALONE, THEN CORTISONE + NaPABA*)

					Control Period on Standard Dose of Cortisone		*Period of Combined Treatment with Cortisone and NaPABA*	
Case	*Age*	*Sex*	*Duration of Disease (yr.)*	*Severity*	*Time (days)*	*Relief (%)*	*Time (days)*	*Relief (%)*
E. R.	69	F	10	4+	30	90	68	90
L. W.	39	M	9	3+	10	100	277	90
J. V.	32	F	2½	3+	7	90	102	90
E. R.	28	F	9	3+	14	90	145	90
A. C.	65	F	20	2+	7	95	78	80
A. C.	37	M	12	4+	14	80	103	80
W. V.	65	M	¾	3+	14	85	79	90
J. O'C.	31	M	7	3+	7	90	106	90
A. W.	56	M	4	3+	7	95	126	80

* Sodium para-aminobenzoate

TABLE 2.—RESULTS IN 6 CASES OF RHEUMATOID ARTHRITIS TREATED BY METHOD 2 (CORTISONE + NaPABA*)

						Duration of Combined Treatment (days)	*Relapse on Placebo Treatment*	
Case	*Age*	*Sex*	*Duration of Disease (yr.)*	*Severity*	*Degree of Relief on Combined Cortisone and NaPABA Treatment (%)*		*Interval (days)*	*Degree*
B. R.	47	F	11	3+	80	128	2	full
O. C.	60	F	⅔	2+	90	85	4	partial
A. M.	38	F	3	3+	90	80	3	full
M. W.	43	F	18	3+	80	88	3	full
R. D'A.	28	F	2	3+	95	114	4	full
E. T.	34	F	11	4+	85	134	4	full

* Sodium para-aminobenzoate

of cortisone acetate. When relief of arthritic manifestations was again established and maintained for variable periods of time, control periods were introduced by the substitution of a placebo for the cortisone.

2. Other patients were started immediately on a single daily intramuscular dose of 25 mg. of cortisone acetate and 12 gm. of sodium para-aminobenzoate were given orally in 8 divided doses of 1.5 gm. at 2-hour intervals during the waking period. When relief of arthritis was well established, control periods were introduced by replacing the cortisone acetate with placebo injections.

All patients were seen at least once weekly during the period of study by one of the authors and both subjective and objective findings were recorded.

Results. Fifteen patients were treated by these methods in the arthritis clinic or in private practice. Table 1 lists the results obtained in 9 patients treated by the first method. Table 2 lists the results obtained in 6 patients treated by the second method.

All the patients treated showed marked improvement both subjectively and objectively. The percentage of improvement recorded is based on the degree of lessening of pain and stiffness and ability to return to work reported by the patient and the observed degree of disappearance of swelling and tenderness recorded by one or more of the observers.

By employing the first method it was possible to compare the improvement of arthritic symptoms and signs obtained on full dosage schedules of cortisone acetate with that noted with a single dose of cortisone acetate of 25 mg. administered intramuscularly and 12 gm. of sodium para-aminobenzoate administered orally in divided doses. The improvement in arthritic manifestations when so compared was the same in 5 cases, somewhat less in 3, and slightly greater in 1 on the combined treatment schedule.

The second method used did not permit comparison of the results obtained with those obtained on full cortisone doses since these patients did not receive more than 25 mg. of cortisone acetate per day at any time. All 6 patients showed marked improvement in their arthritic manifestations. That this was not a coincidence was amply shown by the very rapid reappearance of arthritic signs and symptoms during the control periods when cortisone was replaced by a placebo.

Case Reports. The following case reports are presented to illustrate the response obtained.

CASE 1. J. V., a 32-year old white housewife, was first seen in the arthritis clinic on September 27, 1950. She gave a history of 2½ years of joint pain and swelling which had become progressively worse in spite of various oral and parenteral treatments administered elsewhere. She exhibited fusiform swelling of all proximal interphalangeal joints of both hands, and swelling, heat, and stiffness of both wrists and both knees. At this time the sedimentation rate was 35 mm. in ½ hour and 69 mm. in 1 hour and the blood count showed a moderate hypochromic anemia. She was given 200 mg. of cortisone acetate intramuscularly and then received 100 mg. daily for an additional 6 days. On the seventh day she reported that pain and stiffness had been relieved about 90% and there was no demonstrable swelling of any joint. The daily dose of cortisone acetate was reduced to 25 mg. On the fifth day at this dosage level the patient developed marked pain, and demonstrable swelling of the proximal interphalangeal joints of both hands, the right wrist, and the right knee was present. Sodium para-aminobenzoate was then given orally in doses of 1.5 gm. every 2 hours during the waking period with a total daily dose of 12 gm. in addition to the single daily intramuscular dose of 25 mg. of cortisone acetate. Within 1 week on this schedule there was moderate relief of pain and disappearance of swelling in all joints except the right wrist. At the end of 2 weeks of this treatment the patient was free from all pain and there was no residual swelling of any joint. The patient was able to carry out all her household duties. The cortisone acetate was then replaced by a placebo injection without the patient's knowledge. Within 2 days there was recurrence of pain and stiffness of the proximal interphalangeal joints of both hands and the right knee. The pain and swelling progressed until at the end of 1 week the placebo injection was replaced by corti-

sone acetate in daily doses of 25 mg. By the eighth day of resumption of cortisone the patient reported that she was completely free of pain and swelling. The treatment was continued until January 17, 1951, at which time it was stopped for purposes of evaluation. The patient remained symptom free for 4 weeks and then noted gradual return of pain and swelling in all joints involved.

Case 2. R. D. A., a 28-year old white housewife, was seen in private practice on December 7, 1950. Generalized pain and swelling of the joints, which had begun 2 years previously after an attack of acute tonsillitis and had confined her to bed for 6 weeks, had persisted in spite of physiotherapy, intravenous injections, and a course of chrysotherapy which was abandoned after 3 months because of failure to obtain any relief.

Examination revealed fusiform tender swelling of the proximal interphalangeal joints of both ring fingers, swelling of the metacarpophalangeal joints of both hands, marked swelling and tenderness of the right wrist, and mild swelling of the left wrist. There was subjective pain in both elbows and knees and the right ankle without objective evidence. The sedimentation rate was 18 mm. in ½ hour and 30 mm. in 1 hour.

This patient was immediately started on a single daily intramuscular injection of 25 mg. of cortisone acetate and received three 0.5 gm. tablets of sodium para-aminobenzoate every 2 hours for a daily total dose of 12 gm. At the end of 1 week the only change noted was a decrease of pain while at rest but no objective changes could be found. At the end of 2 weeks of therapy the patient reported marked relief from pain, and the previously noted swelling of the interphalangeal and metacarpo-phalangeal joints had disappeared. After 3 weeks of this treatment the improvement in pain was estimated by the patient to be 80%, since she felt tired and stiff after doing housework all day. After 4 weeks of treatment there was 95% relief from pain, since the only discomfort reported was slight stiffness for about half an hour after arising and there was no objective evidence of joint disease. At this time the daily injection of cortisone was replaced with a placebo. After 4 days of placebo injection the patient reported joint pain and stiffness and the right ankle became visibly swollen, warm, and tender. Pain continued to increase and on the seventh day the placebo injection was replaced with 25 mg. of cortisone acetate. Pain and swelling subsided gradually over a period of 1 week. When last seen on March 22, 1951, the patient felt fine and was able to do all her housework. At this time the sedimentation rate was 8 mm. in ½ hour and 18 mm. in 1 hour. This patient gained a total of 15 pounds during the period of treatment.

Case 3. A. C., a 65-year old white housewife, was seen in the arthritis clinic on September 13, 1950, with a history of rather mild rheumatoid arthritis involving the hands, wrists, elbows, shoulders, and knees of 20 years' duration. About 2 years previously this had become quite severe, especially in the left knee and the right shoulder, and greatly limited her activity. She obtained no relief from a course of gold therapy administered elsewhere. There was slight swelling of the proximal interphalangeal joints of the right hand. The knee joints were warm and swollen and crepitation could be elicited. X-ray examination revealed evidence of osteoarthritis of the knees and hands in addition to the swelling. Treatment with cortisone acetate was begun with an initial dose of 200 mg. which was followed by a daily intramuscular dose of 100 mg. for 6 days. At the end of this period there was a great deal of euphoria and pain and stiffness were almost completely relieved. Slight swelling and warmth to touch could be demonstrated in the left knee. The daily intramuscular dose of cortisone was reduced to 25 mg. and in 5 days there was complete return of pain and stiffness of the previously involved joints with demonstrable swelling and heat in both knees. Sodium para-aminobenzoate administration was then begun in doses of 1.5 gm. at 2-hour intervals for a daily total dose of 12 gm. in addition to the single daily intramuscular injection of 25 mg. of cortisone acetate. On this the patient gradually regained her previous degree of improvement until at the end of 3 weeks of combined treatment she estimated her relief from pain and stiffness to be 90%. At this time there was still some swelling and warmth in her left knee. Roentgen examination of the knees again showed marked osteoarthritic changes in the left knee. Therapy was continued until December 13, 1950, at which time it was stopped. The final estimate of the degree of improvement on the combined therapy was 80%. When last seen in February, 1951, she had no relapse.

Discussion. Studies on these patients demonstrate that the combined use of cortisone and sodium para-aminobenzoate permits satisfactory sub-optimal control of the manifestations of rheumatoid arthritis with an arbitrarily chosen dose of cortisone acetate which

by itself, is completely ineffective in controlling the manifestations of rheumatoid arthritis. The sodium para-aminobenzoate in the dosage employed has produced no evidence of any beneficial results when administered alone.

Careful observation has failed to demonstrate any of the undesirable side effects which are fairly common with the usual dosage schedules of cortisone acetate. The euphoria and subsequent depression so often seen have been completely absent. Edema has not been noted in spite of the relatively high sodium intake due to the sodium para-aminobenzoate given. Moderate gain in weight has been noted, but since most of the patients were at or below optimum weight this has not been troublesome. It was not found necessary to institute any rest periods and it is believed that no marked adrenal cortical inhibition was produced with the doses employed. Aside from mild heartburn, which can be corrected by supplying milk, no toxic reactions to the sodium para-aminobenzoate used were noted.

The additive or synergistic action of cortisone and para-aminobenzoic acid requires further elucidation. The only explanation which can be advanced at this time is based on the similarity in structure and therefore probable similarity of fate in the body of the estrogens and corticosterone. The known inhibition of destruction of the estrogens by the liver by para-aminobenzoic acid suggests one plausible mechanism. Further investigation of this mechanism is certainly indicated and may lead to the discovery of even better synergistic agents. Recent work suggests that the corticosteroids may exhibit their beneficial effects on rheumatoid arthritis by the suppression of the action of some of the intra-cellular enzyme systems[1]. That this effect, at least on hyaluronidase, can be reversed by the addition of sulfhydryls would suggest the possibility that the synergistic effect of cortisone and para-aminobenzoic acid is produced in a similar fashion.

Work now under way tends to prove that the synergism between cortisone and para-aminobenzoic acid exists when both substances are administered orally. Results with oral dosage will form a separate report.

The effectiveness of the combined treatment in these cases warrants further use of this method. At a time when the supply of cortisone is so far short of the demand, a method which spares the amount of cortisone required per patient would seem to be of value.

Summary and Conclusions. The theoretic considerations leading to the trial of the simultaneous administration of cortisone and para-aminobenzoic acid have been presented. The results obtained with the method outlined have been tabulated. They have been comparable with those obtained by the administration of much larger doses of cortisone alone, with the additional advantage of a reduction in reactions. An additive or synergistic action of these two compounds in the treatment of rheumatoid arthritis has been shown. The degree of success obtained in 15 cases warrants further and more extensive use of this method.

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ACUTE NONSPECIFIC PERICARDITIS*

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Nonspecific pericarditis, which is essentially a benign disease, often presents many features closely resembling myocardial infarction. In the past decade there has been increased awareness of this form of pericarditis of unknown etiology, and attention has been directed toward its frequent confusion with coronary thrombosis[2,7,15]. From the standpoints of prognosis and treatment the importance of such differential diagnosis is evident. Because of this frequent confusion, 9 additional cases of nonspecific pericarditis are presented in an attempt to determine factors of value in distinguishing the disease from acute myocardial infarction and other conditions in which chest pain is a prominent feature.

In 1942, Barnes and Burchell[2] described a pericarditis of an acute benign nonsuppurative type, and especially stressed the characteristics which differentiate it from coronary occlusion. During the past 8 years, others have reported cases of acute nonspecific pericarditis and emphasized the relatively benign course and the apparent absence of residua, but point out that the disease may simulate myocardial infarction[3-5,10,12,14].

The 9 patients on whose case histories this report is based were seen during the past 3 years. All patients were male, but this is not considered significant, since the cases came from a veterans' hospital. The age incidence ranged between 24 and 59 with an average of 38 years. The patients were selected to illustrate the varying forms of this disease. The outstanding points of the clinical courses of these patients are presented in the following case reports:

Case Reports. Case 3. T.D.B., 59-year old white man, was admitted to Brown General Hospital on August 13, 1948. Twenty-four hours prior to admission he suddenly developed severe substernal pain with radiation to the left shoulder and the neck. The pain was aggravated by deep respirations and the recumbent position, and the patient found that he was most comfortable in the sitting position. There were associated dyspnea and mild cough.

The physical examination revealed a well developed but poorly nourished white man who appeared moderately uncomfortable but in no acute distress. The temperature was 100.8° F. The respiratory rate was 28; the pulse rate was 108, and the blood pressure was 120/80. The neck veins were slightly distended. The pharynx was injected. Chest examination revealed moist rales over both lung bases and some decrease in the breath

* Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

sounds over the left base posteriorly and laterally. The heart was not enlarged to percussion. A loud pericardial friction rub was heard over the base of the heart. The remaining physical examination was essentially negative except for moderate deformities due to atrophic arthritis. The white blood count was 14,650 with 92% neutrophils. The sedimentation rate was 23 mm. in 1 hour. The red blood count was 5,460,000, with 14.5 gm. of hemoglobin. The urinalysis and serology were negative. A teleoroentgenogram revealed a definitely enlarged heart with widening at the base. The lung fields showed clouding of the left base which was interpreted as probable pleural involvement. The electrocardiogram demonstrated ST segment elevation in all standard leads. The T waves were upright in leads I and II but inverted in lead III. There was a deep Q III pattern.

Because of the severe chest pain and the changes noted in the electrocardiogram the patient was thought to have a posterior myocardial infarct when first admitted to the hospital. He was placed at bed rest and given supportive care. The temperature returned to normal on the 3rd day and by the 5th hospital day the patient was completely asymptomatic. The pericardial friction rub persisted for 2 days. Serial electrocardiograms were taken, and the ST segment elevation returned to the isoelectric line after 1 week. The T waves in the standard leads gradually became flattened.

Two weeks after admission, T waves in I were isoelectric and inverted in II and III, and flat in CF 5 and CF 6. The white blood count returned to normal but the sedimentation rate remained elevated to 26 mm. in 1 hour. A repeat teleoroentgenogram showed the heart to have decreased in size. The pleural involvement of the left base had completely cleared. The patient was discharged, asymptomatic, after 1 month of hospitalization; however, the electrocardiogram still showed the previously described T wave changes.

A follow-up examination was made in September, 1950, at which time the patient gave a history of having been enjoying good health. Recurrence of chest pain or respiratory symptoms had not been noted. A chest roentgenogram, a hemogram, and urinalysis were normal. The electrocardiogram was found to be normal. The previously described Q III pattern was not considered significant in the presence of a normal QRS in aVF.

COMMENT. The difficulty in differentiating acute nonspecific pericarditis from acute myocardial infarction is shown quite clearly in this patient. Many of the classical features of myocardial infarction were present. The patient was in an older age group; the onset, location, and radiation of the pain were fairly typical; fever and leukocytosis were present; and a friction rub developed. Even the initial electrocardiogram on brief analysis was suggestive of coronary occlusion because of elevated ST segments in the standard leads and the presence of a deep Q wave in lead III. The significant points indicating the presence of pericarditis were the relation of chest pain to respiration; the constancy, duration, and intensity of the friction rub; the further evaluation of serial electrocardiograms which demonstrated no Q wave in aVF, indicating the QIII to be positional in origin; and the absence of reciprocal changes of the ST segments.

CASE 6.* A 52-year old white man was admitted to Brown General Hospital on July 11, 1950, with the chief complaint of chest pain. Thirty-six hours prior to admission he experienced severe substernal pain which radiated to the back of the neck, to the left shoulder, and down the left arm to the wrist. This pain was aggravated by respiratory movements. Because of the persistent severity of the pain, the patient was brought to the hospital. The history was negative for previous episodes of chest pain or known heart disease, and no associated or recurrent respiratory infections had occurred.

Physical examination revealed an acutely ill, apprehensive, well-nourished middle-aged male. The temperature was 98.8° F.; the pulse was 84; the respiratory rate was 28 per minute, and the blood pressure was 100/75. There was no cyanosis or distention of the neck veins. The lung fields were clear. The heart sounds were distant in character, and the pulmonic second sound was of greater intensity than the aortic second sound. No murmur, gallop rhythm, or friction rub was

* Reported as Case Report by McCord and Taguchi[8].

heard. The abdomen was slightly distended. The remaining physical examination was not significant. The initial white blood count was 14,600 cells per c.mm. with 75% polymorphonuclear cells. A portable chest roentgenogram demonstrated a heart of normal size and configuration and minimal congestive changes of the left lung base. The electrocardiogram was normal.

The patient was diagnosed as having an acute myocardial infarction and treatment was instituted accordingly. Anticoagulant therapy was started on the evening of admission with full therapeutic doses of heparin and dicoumarin. The prothrombin time was maintained at less than 25% of normal for 14 days. The temperature spiked to 100.8° F. for the first 5 days. The chest pain became less severe on the 2nd hospital day. On the 3rd day a loud pericardial friction rub was heard at the base of the heart. At this time an electrocardiogram showed little change from the initial tracing other than slight elevation of the ST segment in lead I. The pericardial friction rub persisted for 3 days. The patient became asymptomatic and afebrile, and it was felt that the probable diagnosis was nonspecific pericarditis; however, anticoagulant therapy was continued because of dissenting opinions. Serial electrocardiograms demonstrated a return of the minimally elevated ST segment in lead I to the base line, but notching of the T waves appeared in the unipolar and precordial leads. The blood sedimentation rate rose to 33 mm. per hour.

On the 12th hospital day the patient developed weakness, dizziness, and chest pain, and the blood pressure fell to 94/70. This was followed by a supraventricular tachycardia with a rate of 160. Subsequently the patient presented the picture of shock with a blood pressure of 84/70 and a marked pulsus paradoxus. Oxygen, quinidine, and digitalis were given and normal sinus rhythm returned. The general state improved only transiently; shock recurred and mental confusion was noted. On the following day, because of his confused state, the patient removed his oxygen tent, walked to the washroom, collapsed, and died.

Autopsy of the patient revealed gross and microscopic evidence of acute pericarditis with old and recent hemorrhage into the pericardial sac, and there was evidence of increased pressure within the pericardium. The myocardium and coronary vessels were essentially normal.

COMMENT. This case again presented on admission many clinical features suggesting myocardial infarction. Anticoagulant therapy and other routine coronary treatment were instituted. The loud pericardial friction rub and the failure of the electrocardiogram to show changes of myocardial infarction favored the diagnosis of primary pericarditis. The fatal termination suggests the possibility of the detrimental effect of anticoagulant therapy. Postmortem examination showed evidence of acute pericarditis, but hemorrhagic changes in the pericardium with an element of cardiac tamponade were noted.

CASE 5. J.H.S., A 24-year old white man, was admitted to Brown General Hospital February 23, 1948, for the purpose of investigating the cause of cardiac enlargement noted on a recent chest roentgenogram. He had been seen as an outpatient on February 14, 1948, at which time a roentgenogram of the chest was obtained because of the respiratory symptoms. A chronic productive cough and frequent upper respiratory infections had occurred subsequent to an illness with pneumonia in 1943. During the recent episodes of upper respiratory infections, the patient had noticed exertional dyspnea and a constricting sensation in the chest. Roentgen-ray examination showed an enlarged, globular-shaped heart. An electrocardiogram showed elevated ST segments in the standard leads II and III.

Examination on admission revealed a well developed and well nourished young male who did not appear ill. The temperature was 98.6° F., the pulse was 70, and the blood pressure was 145/100 without a pulsus paradoxus. The upper respiratory tract and the lung fields were clear. The heart was not enlarged, the sounds were of good quality, and no murmurs or friction rubs were heard. Teleoroentgenogram and a fluoroscopy at this time showed the heart to be normal in size and in other respects. Electrocardiogram at this time revealed that the previously elevated ST segment had returned to the isoelectric line. Repeat electrocardiograms on this admission were found to be normal with the exception of a tracing taken on March 2, 1948, which revealed auricular tachycardia. The hemogram, urinalysis, and sedimentation rate were normal.

The patient was readmitted to Brown General Hospital on April 16, 1948. One week previously he had developed an upper respiratory infection. Six days prior to admission he

began to have severe stabbing nonradiating precordial pain, not related to exertion, but definitely aggravated by deep respirations. He continued to have paroxysmal attacks of this pain for 3 days. During this time he had a cough associated with chilliness, fever, sweating, and weakness. He did not appear to be acutely ill on admission. The temperature was 99° F., the pulse was 70, and the blood pressure was 118/80 without a pulsus paradoxus. The pharynx and lung fields were clear. The heart was not thought to be enlarged. No murmurs or friction rubs were heard. Teleoroentgenogram again revealed a globular heart. The electrocardiogram showed ST segment elevation in the standard leads II and III. The white blood count was 11,150 with 76% neutrophils. The cold agglutinations and usual febrile agglutinations were negative. The second strength tuberculin test was positive.

The patient was practically free of symptoms on admission and continued asymptomatic and afebrile throughout the hospital course. A chest x-ray taken 5 days later showed a definite decrease in the cardiac size. On serial electrocardiograms, the ST segment deviation returned to the isoelectric line. No significant T wave changes developed.

COMMENT. This patient demonstrates the recurrent nature of the attacks of acute benign pericarditis and the frequently associated respiratory infections.

Discussion. Acute nonspecific pericarditis is generally considered to be inflammatory in nature and infectious in origin, and the latter view is supported by the high incidence of recent antecedent or associated respiratory infections. In other series of cases reported, antecedent respiratory illness occurred in 60 to 85% of the patients with nonspecific pericarditis[6,14]. In 7 of the 9 cases in this study respiratory infection was a prominent feature of the disease. Table 1 summarizes the related respiratory conditions. In 2 of the 4 cases with moderately severe clinical respiratory infection Roentgen-ray evidence of the presence of pulmonary infiltration permitted the diagnosis of atypical pneumonia. In 3 cases there was evidence of pleural inflammation on Roentgen-ray examination.

Pain has always been described as an outstanding symptom of the disease and invariably offers some initial confusion with coronary artery thrombosis.

TABLE 1.—ASSOCIATED RESPIRATORY DISEASE IN 9 CASES OF NONSPECIFIC PERICARDITIS

Case No.	*Present Illness*			*Past History*		
	U.R.I.	*Pneumonia*	*Pleuritis*	*Frequent U.R.I.*	*Pneumonias*	*Pleuritis*
1.			+			+ + + +
2.	+	+	+		+	
3.			+			
4.	+			+ + + +		
5.				+ + + +		+
6.						
7.	+					
8.		+				
9.	+					

U.R.I. = upper respiratory infection.

Chest pain was present in 7 cases as outlined in Table 2. In 6 patients chest pain was a dominant feature, being substernal in location and severe in intensity. In 5 of these cases, there was radiation to the left shoulder; 2 of the patients described the pain as radiating down the left arm to the wrist. In 2 cases there was no chest pain. In 1 of these cases there was persistent aching in the back of the neck, both shoulders, and the left arm to the elbow. In the other there was severe pain in the left shoulder and under the left scapula. The chest pain was very much like that seen in myocardial infarction with the exception of its relation to respiration. In 5 cases there was distinct accentuation of the pain by respiratory movements or by any active or passive movements of the thorax. Carmichael[4] reported that the chest pain was intensified by respiration in 76% of his cases.

A pericardial friction rub may be heard in both myocardial infarction and acute nonspecific pericarditis; however, there appear to be differences which are of distinct value in establishing a correct diagnosis. The pericardial friction rubs associated with nonspecific pericarditis were present earlier, of greater intensity, more constant, and heard over a wider area than those associated with myocardial infarction. Therefore, the presence of a friction rub at the time of the initial pain is an important point in favor of nonspecific pericarditis. In 6 of these 9 cases a loud pericardial friction rub was heard over a wide area of the precordium. In contrast, the friction rub of myocardial infarction is most often transient and localized. A review of previous reports on nonspecific pericarditis shows that a friction rub was heard in about 75% of the cases. Table 3 outlines the auscultatory findings in the present series.

TABLE 2. CHEST PAIN IN 9 CASES OF NONSPECIFIC PERICARDITIS

Case No.	*Presence*	*Severity*	*Radiation to Left Shoulder*	*Aggravated by Respiration*
1.	+	+ + +	+	0
2.				
3.	+	+ + +	+	+
4.	+			+
5.	+	+ +		+
6.	+	+ + + +	+	+
7.				
8.	+	+ + + +	+	0
9.	+	+ + +	+	+

The electrocardiographic changes of nonspecific benign pericarditis have been stressed by most observers as one of the most valuable aids in differential diagnosis[2,11,15]. This is true if classical patterns of infarct or acute pericarditis are demonstrated. The classical changes of acute pericarditis consist of initial elevation of ST segments in 2 or more leads and upright T waves which are occasionally tall or peaked. After a few days or occasionally weeks, the ST segment returns to the isoelectric line and

TABLE 3.—PERICARDIAL FRICTION RUB IN 9 CASES OF NONSPECIFIC PERICARDITIS

Case No.	*Onset*	*Duration (days)*	*Intensity*	*Location*
1.	On Adm.	3	+ + +	Entire Precordium
2.			None Heard	
3.	On Adm.	2	+ + +	Entire Precordium
4.	On Adm.	10	+ + + +	Entire Precordium
5.			None Heard	
6.	3rd Hosp. Day	3	+ + +	Loudest at Base
7.	7 Days Prior to Adm.	4	+ + +	Loudest at Base
8.	5th Hosp. Day	4	+ +	Entire Precordium
9.			None Heard	

the T waves become flattened or frankly inverted. Nay[10] observed that in pericarditis the T wave inversion seldom appeared until the ST segment returned to the isoelectric line. The QRS patterns and reciprocal depression of the ST segments that occur in early or late myocardial infarctions are not observed in acute pericarditis.

TABLE 4.—ELECTROCARDIOGRAPHIC CHANGES IN 9 CASES OF NONSPECIFIC PERICARDITIS

	Present on Admission	*Present during Hospitalization*
Abnormal Electrocardiogram	4	9
S–T Segment Elevation	3	7
T–Wave Inversion	2	9
Arrhythmias	0	2

In the authors' experience the characteristic electrocardiogram changes of nonspecific pericarditis are not found in all cases, especially during the initial period of the illness when early diagnosis is desired (Table 4). The EKG taken at the time of admission or shortly thereafter demonstrated no significant abnormalities in 5 cases. In the 3 cases showing elevation of the ST segments on admission, the elevation was significant primarily in comparison with subsequent tracings demonstrating a return to normal. Inverted T waves were present on admission in 2 cases, but these changes were of little value in making an early specific diagnosis. Although 7 patients showed ST segment elevations and all 9 patients showed T wave inversions during their hospital course, these changes were of diagnostic significance only on evaluation of serial electrocardiograms.

The electrocardiograms in most cases are reported as returning to normal within a 6-week period following the acute phase of pericarditis; however, a few cases will continue to show T wave abnormalities for months or even years[4]. In 1 of the cases of this series (Case 4) T wave abnormalities, consisting of diphasic and inverted T waves

were still present in the standard and precordial leads after a 2-year follow-up.

It is notable that in 2 of 9 cases a paroxysmal supraventricular tachycardia developed during hospitalization. Although not previously stressed, this is apparently not an uncommon occurrence[3,6,15].

More than half of these patients had an elevated temperature on admission; however, there was a history of fever in almost all cases. The fever characteristically heralded the onset of the illness and was frequently present with the initial pain in contrast to the usual later occurrence of fever in myocardial infarctions. The fever rarely exceeded 102° and persisted a few days to 3 weeks. The sedimentation rate was accelerated in all cases, usually returning to normal in 3 weeks. The leukocyte count varied from normal to 14,000 per c.mm. with the differential of the higher counts showing the polymorphonuclear percentage to be increased. Blood tests for cold agglutination were found negative in the 4 cases checked. Blood cultures were carried out in 7 cases and found to be negative.

In 2/3 of the cases the cardiac silhouette was increased considerably in size and roentgenologic follow-up demonstrated in most cases a rapid return to the normal heart configuration. Such degrees of cardiac enlargement are unusual in acute myocardial infarction and the subsequent rapid change in heart size would favor pericardial effusion[1]. In general, clear lung fields in the presence of a huge cardiac silhouette suggest pericardial effusion;

TABLE 5.—DIFFERENTIAL DIAGNOSIS IN NONSPECIFIC PERICARDITIS

Clinical Features	*Nonspecific Pericarditis*	*Myocardial Infarction*
AGE	Average age less than 45 years	Average age above 50 years
SEX	Male to female ratio 3 to 1	Male to female ratio 2 to 1
ANTECEDENT RESPIRATORY INFECTION	Occurs in 60–85% of cases	No significant relation
CHEST PAIN	Aggravated by respirations (75%)	Not usually aggravated by respirations
PERICARDIAL FRICTION RUB	Frequently present (75%)	Present in 15–25% if carefully looked for
	Loud and heard over wide area	Localized
	Long duration	Short duration
CIRCULATORY COLLAPSE	May occur	Common
FEVER	Noted (at onset)	Usually 24–48 hrs. after onset
ROENTGENOGRAM	Heart enlarged in approximately 50% cases with rapid change in size	Heart may be enlarged but rapid change in size rare
	Pulmonary changes if present those of pneumonitis or pleurisy	Pulmonary changes those of congestion
EKG	*ST* segment elevation without reciprocal changes	*ST* segment elevation with reciprocal shifts
	No *QRS* changes	*QRS* changes prominent
	Late *T* wave inversion	
LEUKOCYTOSIS	Present early	Usually later
SEDIMENTATION RATE	Present early in course	Present later in course

however, this sign may be more helpful in tuberculous pericarditis in contrast to the nonspecific pericarditis which is not uncommonly associated with inflammatory changes in the lung.

Levy and Patterson[6] and Carmichael *et al.*[4] consider the increase in cardiac silhouette frequently observed in nonspecific pericarditis to be due to myocardial dilatation; however, some authors feel that pericardial effusion best explains the roentgenologic evidence of increased heart size[9,12]. It appears that more diagnostic pericardial aspirations or angiocardiographic studies will have to be made before a definite conclusion can be reached.

Where aspirations have been done, the fluid has been described as serohemorrhagic[9,12]. The hemorrhagic nature of the pericardial fluid would raise the question of whether anticoagulant therapy might not be contraindicated, further emphasizing the need for differentiating this condition from myocardial infarction.

The significant features which may be helpful in differentiating nonspecific pericarditis from myocardial infarction are summarized in Table 5.

All reports have generally agreed that the prognosis of nonspecific pericarditis is favorable, and there has been ample follow-up to substantiate the benign nature of the disease in most cases[4]. All cases in this series except one (Case 7) presented courses which were in keeping with the usual excellent prognosis.

Summary. 1. Nine case of nonspecific pericarditis are presented.

2. The frequent confusion of this condition with myocardial infarction is stressed.

3. The clinical features which help to distinguish this disease from acute myocardial infarction are: a) chest pain, which is aggravated by deep respirations; b) pericardial friction rub which occurs early and is heard over a wide area; c) associated respiratory infections; d)tendency for recurrent attacks; e) favorable prognosis.

4. The initial electrocardiogram in these cases offered very little positive help in the early diagnosis of nonspecific pericarditis; however, serial electrocardiograms were diagnostic in showing the changes of pericarditis, or aided in a negative sense in militating against myocardial infarction.

5. Three case reports are included to illustrate the varying clinical forms of the disease. Two cases present clinical features simulating myocardial infarction. One of these cases with a fatal termination suggests the possible harmful effect of anticoagulant therapy. One case demonstrated the recurrent nature of nonspecific pericarditis.

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THE RELATION OF THE KIDNEY TO THE ACUTE PRESSOR ACTION OF DESOXYCORTICOSTERONE*

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In a recent study the intravenous injection of desoxycorticosterone acetate (DCA) was found to cause prolonged elevation of the blood pressure of hypertensive but not of normotensive subjects. The pressor effect of DCA could not be attributed to increased cardiac output as measured by the ballistocardiograph, or to vasoconstriction in the ear lobes, fingers, or toes as measured by photoelectric plethysmography[2]. Three possible explanations for its action come to mind: a) that DCA causes renal vasoconstriction, thereby stimulating a renal pressor mechanism, b) that DCA causes an alteration in the fluid compartment of the body leading to an increased blood volume (not found by Perera and Blood[4]), and c) that DCA has a direct action on the smooth muscles of blood vessels. The present investigation is concerned with the first possibility.

Methods. The clearances of sodium p-aminohippurate, mannitol, and chloride were determined in 6 hypertensive, 4 normotensive individuals, and 2 patients with Cushing's syndrome before and after the intravenous injection of either the acetate or glucoside of desoxycorticosterone (DCA or DCG). Solutions for the clearances were made in "physiological" saline solution (0.85%). Blood pressure was measured at frequent intervals during the experiments by the standard cuff method. After 2 control periods of approximately 15 minutes each, 5 mg. of DCA†† in 2.5 cc. of propylene glycol or its approximate equivalent, 10 mg. of DCG dissolved in 1.0 cc. of 10% glucose and 10% acetamide, were injected intravenously. The effects were observed during 1 to 5 subsequent periods. In 3 instances, the effects of propylene glycol alone were measured. The daily dietary intake of salt was 5 to 8 gm. for all subjects except V.R., a hypertensive subject receiving 1 gm. per day on 1 occasion and 16 gm. on another. In an attempt to standardize psychogenic influences all experiments were done under the same environmental conditions.

Ten healthy mongrel dogs, 4 female and 6 male, were anesthetized with pentobarbital sodium (0.029 gm. per Kg.) and a Hamilton optical manometer was used to record blood pressure in the femoral artery photokymographically. Adequate control injections of

* This work was done under a grant-in-aid from the U. S. Public Health Service.
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either propylene glycol (the solvent for DCA) or 10% glucose in 10% acetamide (the solvent for DCG) were made intravenously and their effect upon blood pressure recorded for several minutes. Subsequently 5 mg. of DCA in 0.5 cc. of propylene glycol, or 5 mg. of DCG in 0.5 cc. 10% glucose in 10% acetamide, were injected. The blood pressure was recorded at 5-minute intervals for a period of at least 15 minutes. Bilateal nephrectomy was then carried out under aseptic technique during the next 15 to 30 minutes. After removal of the kidneys, injections of the same substances were again made in the same order. Twenty-four or 48 hours later the experiments were again made in the same order. Twenty-four or 48 hours later the experiments were repeated under anesthesia in the 6 dogs which were in good condition. The dogs were maintained on a meat-free diet after nephrectomy. Average levels of blood pressure were used for calculations.

TABLE 1.—EFFECT UPON RENAL CLEARANCES AND BLOOD PRESSURE OF DCA AND DCG GIVEN INTRAVENOUSLY

Subject	Date 1948	Substance**	C_{pah} Control	C_{pah} After	C_m Control	C_m After	Filtration Fraction Control	Filtration Fraction After	Periods After Control	Average Blood-pressure Control	Average Blood-pressure After	Remarks
HYPERTENSIVE												
D. B. ♀	3-29	DCA	485	341	110	83	.23	.24	4	146/96	158/113	
	4-16	PG	452	342	91	72	.20	.21	2	150/100	152/110	
		DCA	342	327	72	72	.21	.22	1	150/100	174/122	
V. R. ♀	3-31	DCA	316	319	83	70	.27	.22	4	190/110	185/112	1 gm. NaCl diet
	4-21	PG	382	420	109	98	.28	.23	2	180/120	202/116	16 gm. NaCl diet
		DCA	420	331	98	88	.24	.27	4	202/116	195/128	
E. C. ♀	4-30	PG	326	269	81	66	.25	.24	2	200/106	200/114	8 gm. NaCl diet
		DCA	269	293	66	73	.24	.25	4	200/106	224/124	
L. S. ♀	5-18	DCG	407	421	90	87	.22	.21	5	178/94	200/101	
	9-24	DCG	—	—	102†	102†	—	—	3	168/94	169/104	
M. H. ♀	10-1	DCG	195	227	42†	52†	.21	.23	3	258/136	227/121	Rt. nephrectomy
I. E. ♀	10-11	DCG	344	464	86†	92†	.25	.20	2	140/88	144/87	Febrile reaction
CUSHING'S SYNDROME												
F. B. ♀	5-21	DCG	559	461	109	102	.20	.22	4	122/88	150/120	
L. P. ♀	5-28	DCG	412	372	91	89	.22	.24	2	114/68	127/79	
NORMOTENSIVE												
G. G. ♀	6-15	DCG	600	610	98	100	.16	.17	3	100/58	102/64	Chronic bronchitis
A. S. ♂	6-21	DCG	591	516	97	89	.16†	.17	3	108/68	117/76	? Scurvy
V. S. ♀	6-25	DCG	543	544	87	88	.16	.16	3	110/68	107/71	Rheum. Arthritis
R. K. ♂	10-5	DCG	812	701	117†	94†	.15	.14	3	124/64	146/80	Conval. poliomyelitis

** PG—propylene glycol; DCA—desoxycorticosterone acetate; DCG—desoxycorticosterone glucoside.
† Sodium thiosulfate used instead of mannitol.
Values are averages of all measurements made in each period.
DCA was given in 5.0 mg. doses, DCG in 10.0 mg. doses.
C_{pah} = sodium p-aminohippurate; C_m = mannitol.

Results. PATIENTS. No consistent effects upon effective renal plasma flow, glomerular filtration rate, or filtration fraction in either the hypertensive or normotensive subjects were noticed (Table 1). When a significant* rise in blood pressure did occur in some hypertensive patients (4 of 6), it could not be correlated with efferent arteriolar constriction as indicated by a significant increase in the filtration fraction. A rise in blood pressure may have occurred in the other hypertensive patients, not demonstrable by the auscultatory method, which in neurogenic hypertension may be subject to wide variations and is not so accurate as methods involving direct puncture[5]. In 2 patients exhibiting Cushing's syndrome, DCG appeared to change the filtration fraction slightly in a direction indicating increased efferent arteriolar constriction concurrent with an increase

* A significant rise was considered to be one of 10 mm. Hg or more in diastolic pressure from the average of the control period determinations.

in blood pressure. There was a significant elevation of blood pressure without change in the filtration fraction in 1 normotensive patient who was convalescing from poliomyelitis. ERPF fell in 7 instances, rose in 3, and was relatively unchanged in 5. Significant elevation of the diastolic pressure accompanied the fall in ERPF in every instance but 1. When diastolic pressure did not change, the clearance of PAH was unchanged or rose. When diastolic pressure rose slightly (4 instances), ERPF fell in 2.

It is of interest that a pressor response to DCA was not elicited in 1 subject, V.R., receiving 1 gm. of salt per day but did occur after she had been ingesting 16 gm. per day; the filtration fraction also tended to increase slightly. The latter change was not seen in subjects ingesting normal diets.

Plasma chloride levels increased in 2 of 3 hypertensive subjects and in both patients with Cushing's syndrome soon after the injection of DCA or DCG, the greatest rise noted being 4.3 mEq./L. in 30 minutes. No such effect was observed in normotensive patients. The urinary volume decreased in 3 of 4 hypertensive subjects and did not change in the others. The chloride excretion increased in 1 hypertensive and the 3 normal patients, decreased in 3 hypertensive patients and 1 with Cushing's syndrome*. The ratio $\frac{U}{P}M - / \frac{U}{P}Cl -$†, which is indicative of the amount of chloride reabsorbed by the tubules, was altered in a direction suggestive of decreased reabsorption only in the "normal" patients. Propylene glycol did not change the rates to any extent in one hypertensive subject. In the others, these steroid compounds either produced no significant change, or in the case of the patient receiving a low-salt diet, increased reabsorption moderately (Table 2). The effects upon chloride excretion are not explained. The assumption of maximal rates of reabsorption by slightly damaged (ischemic) renal tubules is inconsistent with the clinical conditions of the patients.

Dogs. Five of the 10 dogs exhibited a pressor response to DCA or DCG before nephrectomy (Table 3) which was not related to the initial levels of blood pressure. Two of 3 showed pressor responses to propylene glycol and none of 4 to glucose and acetamide. Immediately after bilateral nephrectomy, 5 of the 10 had a similar pressor response. Twenty-four hours later 2 of 4 gave a pressor response and 48 hours after nephrectomy, 1 of 3 again responded. A pressor response occurred after nephrectomy in 2 instances in which it had

* It is possible that the patient, L. P., who exhibited Cushing's syndrome, did not represent a classical case, especially in view of the absence of the effect of DCG on urinary chlorides.

† The urine mannitol concentration, designated $\frac{U}{P}M -$ represents the degree to which the glomerular filtrate is concentrated, assuming mannitol is not reabsorbed by the tubules. $\frac{U}{P}M - / \frac{U}{P}Cl -$, actually the ratio of the clearances of mannitol and chloride, has been termed the "chloride reabsorption ratio."[3] The clearance of mannitol was considered a measure of the glomeruler filtration rate, and therefore an indication of the amount of chloride filtered. The ratio must therefore always amount to 1 or more; in normal states values of 50 to 100 or more are the rule, varying with the dietary intake. High values indicate high relative rates of reabsorption, low values indicate that more chloride is excreted.

TABLE 2.—EFFECT UPON CHLORIDES AND URINARY VOLUME OF DCA AND DCG GIVEN INTRAVENOUSLY

Subject		1948	Substance*	Plasma Chlorides mEq./L.		Urine Chlorides mEq./L.		Urine Volume cc./min.		$\frac{U}{P}\frac{M-Cl-}{P}$†		Daily Dietary NaCl Gm.
				Control	After	Control	After	Control	After	Control	After	
HYPERTENSIVE												
D. B.	♀	3-29	DCA	104	104	.47	.36	4.5	3.0	25	24	5-8
V. R.	♀	3-31	DCA	103	105.5	.13	.08	4.3	1.9	65	92	1
V. R.	♀	4-21	DCA			.82	.57	6.5	4.5	—	—	10
L. S.	♀	5-18	DCG	106	107	.34	.40	3.9	4.2	28	24	5-8
D. B.	♀	4-16	PG	104	105	.38	.29	3.5	2.7	25	28	5-8
CUSHING'S												
F. B.	♀	5-21	DCG	101	103	.43	.34	4.2	3.7	26	31	5-8
L. P.	♀	5-28	DCG	114.6**	116.3	1.14	1.14	6.8	6.7	9	9	5-8
NORMOTENSIVE												
G. G.	♀	6-15	DCG	103.7	104.1	.11	.19	2.1	2.4	98	51	5-8
A. S.	♂	6-21	DCG	100.8	101.1	.23	.28	2.8	3.1	42	32	5-8
V. S.	♀	6-25	DCG	103.3	101.5	.22	.44	2.4	2.8	43	27	5-8

* DCA was given in 5.0 mg. doses, DCG in 10.0 mg., and propylene glycol (PG) in 2.5 ml. doses.
† See page 259 for explanation of ratio.
** 400 cc. of 5% NaCl given I.V. before experiment.
Values are averages of 2 or more measurements made in control and experimental periods.

TABLE 3.—EFFECT ON BLOOD PRESSURE (MM.HG) OF INTRAVENOUS DCA AND DCG BEFORE AND AFTER BILATERAL NEPHRECTOMY

Dog	Sex	Subst.*	Control		Post-nephrectomy		24 hr. Post-nephrectomy		48 hr. Post-nephrectomy	
			B.P.†	Response**	B.P.	Response	B.P.	Response	B.P.	Response
1.	♀	DCG	160/118	0	118/84	+	108/57	+++		
2.	♂	DCG	140/85	0	140/85	0	shock			
		G. A.	140/85	0						
3.	♀	DCG	180/100	+	131/85	++++	shock			
		G. A.			125/82	++				
4.	♀	DCG	180/140	+	134/110	++	175/115	0		
5.	♂	DCG	195/120	++++	200/132	+	200/125	+++	202/125	0
		G. A.	230/145	0						
6.	♂	DCA	210/132	0	220/145	0				
		P. G.	237/155	+++	245/150	0				
7.	♂	DCA	162/105	0	180/125	0	—	—	215/135	+
		P. G.	185/127	+++	195/135	0			215/135	0
8.	♀	DCA	170/110	+++	175/112	0				
		P. G.	175/117	0	175/125	+				
9.	♂	DCG	170/85	++	150/98	+	—	—	120/63	0
		G. A.	170/85	0	150/98	0			120/63	0
10.	♂	DCG	180/115	0	145/95	0	120/55	0		
		G. A.	180/115	0	145/95	0	125/60	0		

* DCG = 5mg. desoxycorticosterone glucoside, DCA = 5 mg. desoxycorticosterone acetate, G. A. = 0.5 cc. 10% glucose in 10% acetamide, P. G. = 0.5 cc. propylene glycol.
† B. P. 15 minutes after injection of substance.
** 0 response = diastolic 0 to 10; + = 10 to 15; ++ = 16 to 20; +++ = 21 to 25; ++++ = 26 to 30 mm. Hg. or higher.

not occurred before. Ordinarily, if desoxycorticosterone caused an elevation of blood pressure in the control period, elevation also occurred after nephrectomy. There was no consistent potentiation or decrease in the response to DCA or DCG immediately after nephrectomy, 3 increasing, 3 decreasing, and 4 not changing. Following nephrectomy diastolic pressures were lower in 4, did not change in 2, and were higher in 4. Three of the 10 dogs exhibited diastolic pressures of 120 mm. Hg or more at the start of the experiments.

Discussion. From these results it is obvious that regular changes in intrarenal hemodynamics do not follow the intravenous administration of DCA or DCG to human subjects. At the most, efferent arteriolar constriction can be postulated. The concomitant rise in diastolic pressure suggests that arteriolar constriction in the kidneys is part of a generalized process and is not confined to the renal vascular bed.

It would also appear that the pressor effect of DCA or DCG when it occurs in dogs does not depend upon the presence of the kidneys. Since there was no consistent potentiation in the pressor response immediately, 24 hours, and 48 hours after nephrectomy, it would seem that removal of an "anti-desoxycorticosterone" substance did not occur.

Davis and others did not find any differences in the pressor action of DCA dissolved in propylene glycol and propylene glycol itself in hypertensive and normal unanesthetized dogs as measured by direct arterial puncture with a mercury manometer[1]. However, changes in the blood pressure may be of such nature that measurements of mean pressure will not give the true picture of what is taking place[6]. For example, in dog experiment one, after nephrectomy the systolic pressure was 118 mm. Hg and the diastolic 84, increasing to 122 systolic and 97 diastolic after the injection of DCG. Change of mean pressure from 101 to 110 would have been considered insignificant, whereas the actual change in diastolic pressure was 13 mm. Hg. Likewise, distorted interpretations may occur in the opposite direction. A change from 108 mm. Hg systolic and 57 diastolic to 175 systolic and 80 diastolic gave an increase in mean pressure of 45 mm., whereas the actual diastolic elevation was 23 mm. If mean pressure readings had been used, a negative instead of a positive response would have been recorded in 4 other instances.

Propylene glycol is an irritating substance when injected rapidly into a vein, causing considerable pain along the course of the vein which may give rise to pressor responses. DCG in the appropriate solvent is not irritating. In 11 of 19 injections into dogs, DCG caused elevation of blood pressure, sometimes of marked degree; in man this response occurred in only 3 of 10 experiments. The inconsistency of response is unexplained. DCA, on the other hand, was pressor in all 3 hypertensive patients, but in only 2 of 7 injections in 3 anesthetized dogs. It is possible that the immediate effects of DCA and DCG differ in both human subjects and dogs. In a few experiments in hypertensive dogs, both anesthetized and unanesthetized, DCA or DCG consistently caused pressor responses while propylene glycol alone injected very slowly did not.

Summary. Measurements of effective renal plasma flow and glomerular filtration rate before and after intravenous administration of desoxycorticosterone acetate and desoxycorticosterone glucoside in 6 hypertensive and 4 normotensive subjects showed no consistent effects on renal hemodynamics. In 2 patients with Cushing's syndrome, slight efferent arteriolar constriction occurred concurrent with an increase of

blood pressure. This occurred in only one of the other subjects. A pressor response in 4 of 6 hypertensive patients and 1 normotensive was observed. As indicated by the ratio $\frac{U}{P}M - / \frac{U}{P}Cl -$, the reabsorption of chloride decreased in normotensive and was unchanged or increased in hypertensive patients and those with Cushing's syndrome. The intravenous injection of 5 mg. of DCA or DCG caused pressor responses in only half of 10 normal dogs. Removal of both kidneys did not affect the responses; that is, if a pressor response occurred prior to nephrectomy, it usually was elicited after nephrectomy. It appears, therefore, that desoxycorticosterone in the doses employed does not cause the pressor response, when it occurs, by initiating a renal vasopressor mechanism dependent upon efferent arteriolar constriction.

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SIGNIFICANCE OF QT PROLONGATION IN THE ELECTROCARDIOGRAM: BASED ON THE STUDY OF 168 CASES*

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Although prolongation of the QT segment of the electrocardiogram has interested the cardiologist for many years, the recent renewed interest in electrolytes and their electrocardiographic effects has stimulated further investigation of this subject. Because the QT interval prolongation is an accompaniment of many different clinical states and since recent studies have disclosed additional conditions which are factors in its production, it seemed of value to accumulate a series of cases manifesting QT segment prolongation as routinely observed in a large hospital to determine a) the various clinical states that are responsible for its causation, b) their relative incidence, and c) the method that may be used to determine the underlying etiology so that proper therapy, if indicated, may be applied.

Material and Methods of Study. The material utilized in the study consisted of the authors' observations on 168 patients with QT segment prolongation. Only those subjects were chosen for study whose electrocardiograms manifested a QT segment prolongation of 20% above the normal as calculated by Bazett's formula[7]. The etiologic classification of these patients is listed in Table 1. In

TABLE 1.—CLINICAL CONDITIONS ASSOCIATED WITH QT PROLONGATION

	Cases
1. Electrolyte Disturbances	
A. Hypocalcemia	
1) Postthyroidectomy	3
2) Idiopathic hypoparathyroidism	1
3) Uremia	15
4) In association with alkalosis accompanying vomiting states	5
B. Hypopotassemia	
1) Diabetic Acidosis	35
2) Vomiting due to intestinal obstruction	34
3) Miscellaneous Group	
a) Familial periodic paralysis	1
b) Inanition	2
c) Adrenocorticotrophic hormone	1
d) Colitis	2
e) Prolonged administration of parenteral fluids (Sodium chloride and glucose)	2
f) Renal disease ("salt-losing nephritis")	2
C. Combined Hypopotassemia and Hypocalcemia (5 cases noted in *A*-4)	
2. Myocardial Abnormality and/or Disease	
a) Hypertensive cardiovascular disease	3
b) Myocarditis	16
c) Myxedema heart	1

* This work was aided by a grant from the United States Public Health Service.

3. Conditions Associated with Myocardial Anoxia	
a) Myocardial infarction	11
b) Arteriosclerotic heart disease	2
c) Pulmonary embolism	5
d) During emergence from Stokes-Adams attack	1
e) In association with illuminating gas poisoning	1
f) Dying heart	2
4. Combined Factors	
a) Hypoglycemia	6
b) Avitaminosis	3
5. Drugs—Quinidine	8
6. Unknown Etiology	6
	168

most of these subjects the opportunity was afforded of taking serial tracings over a period of days. In the patients with hypocalcemia, hypopotassemia, and electrolyte alterations due to fluid loss, frequent chemical estimations were made, including pH, carbon dioxide-combining power, protein, chloride, urea nitrogen, potassium, and calcium, simultaneously with the taking of the electrocardiogram. In the earlier group of patients only the limb leads I, II, and III were taken. In the majority, however, leads CR 2, 3, 4, and 5 in addition to the limb leads were available. In 5 patients with hypocalcemia and 40 patients with hypopotassemia, electrocardiographic and chemical estimations were made before, during, and after administration of these electrolytes.*

In those instances where multiple electrolyte alterations were present, studies were made during and after the administration of the respective ions.

Determinations of the electrolyte concentration in the serum were also obtained on some patients in whom the QT segment prolongation was associated with coronary occlusion, pulmonary emboli, rheumatic fever, hypertension, and the administration of quinidine sulfate. Since the results were largely negative, such estimations as a routine measure were later abandoned.

The serum potassium, calcium, and sodium determinations were performed with a Beckman flame photometer. At least 1 specimen of each group of calcium determinations was checked independently by the Clark and Collip method[19]. Phosphates were determined by the method of Fiske and SubBarow[33], chloride by the method of Wilson and Bell[71], carbon dioxide-combining power by the method of Van Slyke and Cullen[67], and the total proteins by the method of Kingsley[47]. Ionizable calcium was determined from the chart of McLean and Hastings[49]. The pH was determined by the Beckman pH meter using the hypodermic type of glass electrode.

The Measurement of Electrical Systole. The measurement of the length of the QT interval is not always a simple matter because the end of the T wave is frequently not clearly demarcated. In this study precordial leads CR 2, CR 3, and CR 4 were used for this measurement, as the authors[11,13,54] have found that these leads give the clearest and most marked evidence of hypopotassemia. That lead in which the termination of the T wave was most clearly seen, and where the QT interval was longest, was used for the measurement.

Another complicating feature in the measurement of electrical systole was the presence of a more or less prominent U wave which followed the T wave at various intervals. It appeared in the form of a T wave notching, or followed the T wave with an intervening depression which did not reach the isoelectric line (Fig. 1). In these tracings it is a matter of some importance whether electrical systole should be measured to the end of the T wave (QT interval) or to the end of the U wave (QU interval)[11,13]. This subject is discussed in another portion of this paper.

Findings. QT Segment Prolongation Associated with a Low Serum Calcium. The etiologic types observed in the patients of this series are noted in Table 1. The serum calcium levels in the patients following thyroidectomy which inadvertently included parathyroid tissue was only moderately lowered. The values were 3.4, 3.5 and 3.7 mEq./L., respectively. Manifestations of mild tetany observed in these patients disappeared following the administration of calcium.

There was one case of idiopathic hypoparathyroidism which fulfilled the criteria established by Drake, Albright, Bauer, and Castleman (1939)[23]. These

* A low serum magnesium is also said to prolong the QT segment. However, relatively few studies are available in the human subject. In the few patients where serum magnesium studies were obtained in patients with hypopotassemia, no significant changes were observed.

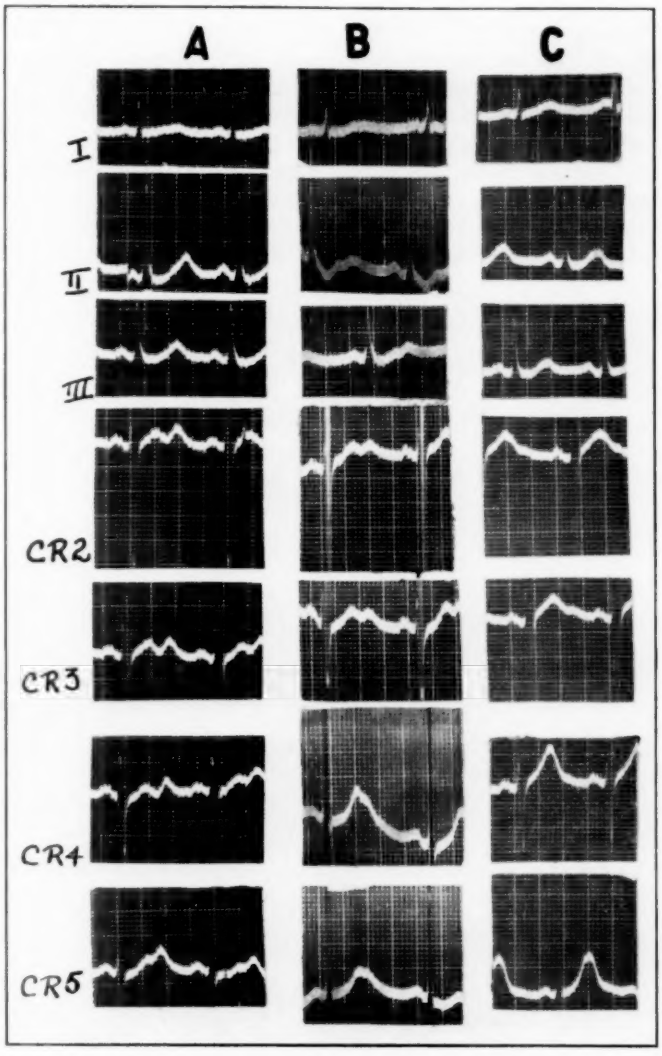

FIG. 1.—D. K., male, age 60. Diagnosis: carcinoma of the head of the pancreas with fluid loss due to vomiting for 3 days prior to admission on Feb. 14, 1950. QT (QU) prolongation associated with hypopotassemia. Note prominent U waves in the control tracing, particularly marked in the precordial leads.

A. Feb. 14, 1950. QU prolonged 72% above normal. Serum potassium was 2.10 mEq./L.

B. Feb. 15, 1950. After 1000 cc. of potassium chloride were given intravenously in 6 hours. Note marked improvement. QT interval prolonged 57%. Serum potassium was 3.35 mEq./L.

C. Feb. 16, 1950. Potassium therapy continued. QT interval now only 16% above normal. Serum potassium was 4.15 mEq./L.

criteria are: a) hypocalcemia, b) increase in organic phosphorus, c) absence of renal disease as the cause of hyperphosphatemia, d) normal roentgenograms of the bones to rule out rickets or osteomyelitis. (Such cases are not common. These authors collected 8 cases from the literature and added 5 cases of their own). The authors' patient, a female, aged 56, presented herself with obscure convulsive seizures which were initially considered to be hysterical in origin. It is of some interest that the diagnosis of hypocalcemia was suggested by the QT prolongation (35% above the calculated normal) in

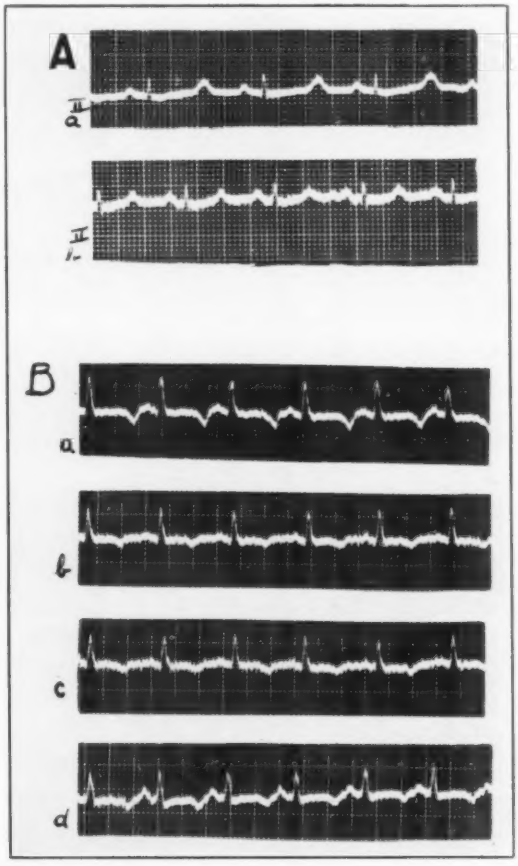

FIG. 2.—A. White female, age 56. Diagnosis: idiopathic hypoparathyroidism. *a*, April 23, 1938. Serum calcium 2.8 mEq./L., serum phosphorus 6.2 mg. 1/100 cc. QT interval increased 30% above predicted normal. *b*, May 16, 1938. After treatment. Serum calcium 4.0 mEq./L. QT interval within normal range.

B. M.D., white male, age 40. Diagnosis: glomerulonephritis with azotemia, renal rickets confirmed by necropsy. *a*, Lead I: QT prolonged 57% above the predicted normal. Serum calcium 2.1 mEq./L.; 20 cc. of 10% calcium gluconate was given intravenously after which tracings were taken at intervals of ½ minute. *b*, 1½ minutes after calcium. Note decrease in length of the QT interval and less inversion of the T wave. *c*, 2 minutes. The QT interval is slightly more prolonged than in *b*. *d*, 15 minutes after injection of calcium. The QT interval increased to 57% which is the same as control *a*.

the electrocardiogram. The serum calcium at the initial observation was 2.1 mEq./L. and phosphorus 7.8 mg. per 100 cc. This patient improved upon the administration of calcium, vitamin D, and parathormone (Fig. 2A).

Prolongation of the QT interval was observed in 15 patients manifesting varying stages of uremia. In addition, the electrocardiograms in most of this group showed inversion of the T waves in the limb leads and in precordial leads taken from the left side of the precordium. Necropsies obtained in 11 patients of this series revealed glomerulonephritis in 6, benign nephrosclerosis in 3, malignant nephrosclerosis in 1, and pyelonephritis in 1. The serum calcium obtained in 8 of these patients ranged from 2 to 3.7 mEq./L. with an average of 3.0 mEq./L.

Of 20 patients with vomiting due to acute intestinal obstruction where frequent serum calcium estimations were obtained, the serum calcium level was diminished in 5. When the serum potassium values were quite low (1.7 to 3.3 mEq./L.), usually associated with a considerable degree of alkalosis, the serum calcium levels also tended to be low but not nearly so low proportionately as the serum potassium. The serum calcium levels ranged between 3.5 to 4.0 mEq. L. in most of the pa-

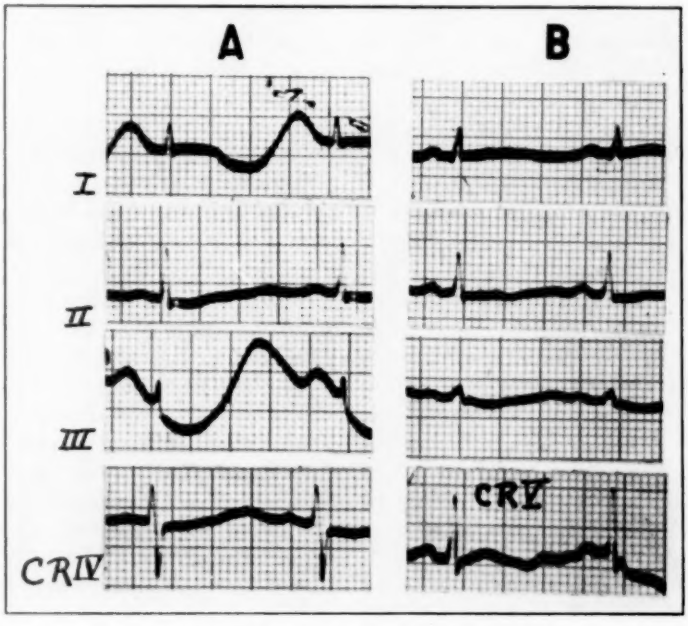

FIG. 3.—Female, age 63. Diagnosis: carcinoma of the stomach.

A. Oct. 17, 1949. Leads I, II, III, and CR4 taken after patient had sustained marked fluid loss by vomiting and through an intestinal fistula. Circulatory collapse was present at this time. The serum potassium was 2.2 mEq./L., CO_2 was 96 vol./100 cc. Note marked prolongation of QT interval in leads I and CR4. QT interval is prolonged 100% above the calculated normal.

B. After patient had received 1000 cc. of isotonic potassium chloride intravenously. Serum potassium was 3.2 mEq./L. Note shortening of QT interval as compared to tracing taken the previous day.

tients when the serum potassium was low. This decrease involved the ionized as well as the unionizable fraction.

THE CHARACTERISTICS OF QT SEGMENT PROLONGATION DUE TO HYPOCALCEMIA. The characteristics of the T wave in QT interval prolongation resulting from hypocalcemia have been discussed by Hegglin and Holzmann[41] and Ernstene and Proudfit[27]. In hypocalcemia prolongation of the QT segment involves only the segment between the QRS and T wave proper, which is an isoelectric line. The T wave itself is apparently unaltered; it may be either inverted or upright. This pattern can usually, but not invariably, be differentiated from hypopotassemia. One of the authors[13] has encountered tracings in patients with alkalosis associated with vomiting states (Fig. 1, pattern IIIb), in which it is difficult on the basis of the electrocardiographic findings alone to differentiate the QT prolongation resulting from these 2 types of electrolyte disturbances[12]. When simultaneous deficiency of calcium and potassium are present the T wave and ST segment changes are frequently atypical. The administration of one or the other electrolyte will often more clearly demonstrate the deficiency of the other electrolyte[14].

EFFECT OF CALCIUM ADMINISTRATION. The intravenous administration of calcium gluconate, 10 to 20 cc. of a 10% solution, will result in more or less complete disappearance of electrocardiographic evidence of hypocalcemia (Fig. 2). This effect is transient and is observed in about 1 to 2 minutes following its administration, with a return to the control configuration in about 5 to 8 minutes. In 4 patients with hypocalcemia no significant alteration in the T wave was observed following the administration of calcium if the hypocalcemic T wave was upright. However, when the hypocalcemic T wave was inverted, the inversion tended to become less deep following calcium administration (Fig. 2B).

The administration of calcium did not alter the QT segment prolongation due to hypopotassemia and vice versa. These electrolytes are apparently specific in compensating for their own deficiency[12], as demonstrated electrocardiographically. It is of some interest that in combined calcium and potassium deficiency the usual evidence of nervous irritability due to hypocalcemia may not be observed. However, after potassium administration the tetany of hypocalcemia becomes manifest[25].

THE QT PROLONGATION ASSOCIATED WITH HYPOPOTASSEMIA. The QT prolongation associated with hypopotassemia is probably the most important single type encountered. This statement is made because of 1) its relative frequency, 2) the profound systemic effects resulting therefrom, and 3) the relatively rapid return to normal of clinical and electrocardiographic alterations following the administration of this ion.

The incidence of the clinical conditions associated with hypopotassemia observed in this series is mentioned in Table 1. They occurred chiefly in patients following treatment of diabetic acidosis and in alkalosis due to vomiting states. This series has been the subject of a separate report on the electrocardiographic manifestations of hypopotassemia[13]. The QT interval was prolonged in 33 of the 35 patients during the stage of hypopotassemia following therapy for diabetic acidosis, in all of the 34 patients with vomiting due to intestinal obstruction, and in all 10 of the cases in the miscellaneous group (Table 1). Correlation between the level of the serum potassium and the degree of QT segment prolongation (QT_c)[65] was made in 42 electrocardio-

grams from patients with diabetic acidosis and in 38 from patients with vomiting. The statistical correlation between the length of the QT interval and the serum potassium concentration was reported previously in a series of cases of diabetic acidosis and was found to be highly significant ($r = 0.73$: $p = <0.001$). The same correlation studies were performed on the present series of cases of diabetic acidosis and showed similar correlations. The statistical correlation between the QT interval corrected for rate (QT_c) and the serum potassium concentration in cases of fluid loss due to vomiting ($n = 38$) has also been found to be significant ($r = -.67$: $p = <<< 0.001$).

U waves of varying degrees of prominence were observed in 33 of 79 patients (42%). The presence of this wave is considered to be an important criterion of hypopotassemia.

The electrocardiographic alterations observed in hypopotassemia were immediately reversed following the administration of potassium.

Myocardial Abnormality and/or Disease: Of 20 cases classified under myocardial disease the etiology was as follows: hypertension in 3, myocarditis in 16, and myxedema in 1 case. The following etiologic types of myocarditis were noted: rheumatic fever in 13, and, in 1 case each, diphtheria, streptococcic infection, and scarlet fever. In addition to QT prolongation, other evidences of myocardial damage as shown by the electrocardiogram were inversion of T waves in limb and precordial leads, abnormalities in the QRS complex, and bundle branch block in 1 case.

The patient with myxedema was a female, aged 40, who was known to have had this condition for about 6 years. The BMR ranged from — 35 to — 40%, the cholesterol was 380 mg. per 100 cc., and the serum calcium (4.6 mEq./L.) and potassium 4.5 mEq./L.) were normal.

Conditions Associated with Myocardial Anoxia. *A. Acute Myocardial Infarction.* Prolongation of the QT interval in myocardial infarction was observed in 11 patients during the acute and subacute stages (Fig. 4). In the healed stage, significant QT prolongation was rarely observed. The incidence of QT prolongation was about equally distributed in subjects with anterior and posterior myocardial infarction.

B. Pulmonary Embolism. QT segment prolongation was observed in 5 subjects with pulmonary embolism. The QT prolongation was considerable, ranging from 33 to 55% above the predicted values. Other evidences of myocardial anoxia, as indicated by ST segment deviation and T wave inversion, were also present. In 3 of these cases the diagnosis was confirmed by autopsy. In the other 2 cases the clinical diagnosis was clear cut; in this latter group the QT prolongation disappeared with improvement of the patient.

C. During Emergence from Stokes-Adams Attack. During a Stokes-Adams attack the heart muscle is subject to extreme degrees of anoxia. In such instances one may occasionally note prolongation of the QT interval in the cycles immediately following an attack of cardiac standstill. As the anoxia diminishes with the return of normal ventricular contraction, the prolonged QT interval gradually decreases and finally returns to normal. Such an episode is illustrated in Fig. 5.

D. In Association with Illuminating Gas Poisoning. The effects of carbon monoxide poisoning in producing myocardial anoxia are well known. A patient 53 years of age who was admitted to the hospital with a severe grade of luminating gas poisoning was studied.

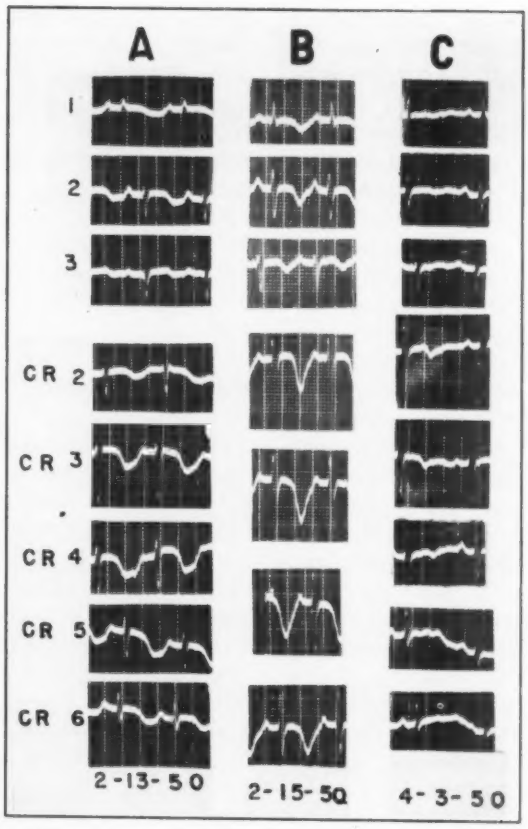

FIG. 4.—Shows QT prolongation associated with acute myocardial infarction. A female, age 54, presented a typical story of substernal and precordial pain accompanied by a state of shock on Feb. 13, 1950.

A. Note inversion of T wave in leads I and II and precordial leads. Also note marked prolongation of QT segments (57% above predicted normal).

B. Taken 2 days later. Note inversion of T wave in all leads with increased amplitude of T waves with QT prolonged 50% above normal.

C. Taken April 3, 1950. The myocardial infarct is now in a subchronic stage. Note marked improvement in tracing. The T waves in leads I and II are still slightly inverted; the T waves are inverted in CR2, 3, 4, and 5. The T wave in CR6 is upright. The QT interval is now within the normal range.

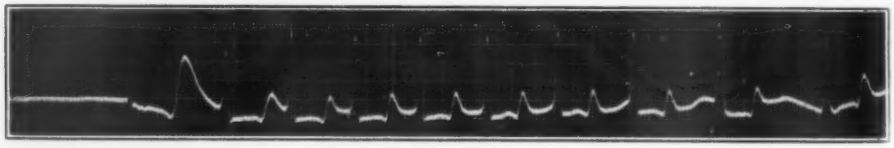

FIG. 5.—Recovery from a period of complete cardiac standstill during a Stokes-Adams syndrome (Lead II). Note long QT interval covering almost entire cycle in first complex after cardiac standstill. Note gradual decrease of QT interval during period of recovery.

The electrocardiogram showed ST segment depression in both limb and precordial leads with marked prolongation of the QT segment. Necropsy showed areas of necrosis involving particularly the subendocardial portion of the left ventricle.

Combined Factors. Hypoglycemia and avitaminosis have been placed in this category. A combination of many factors is apparently operative in producing the QT prolongation in these states. These will be discussed below.

Hypoglycemia. Of 58 electrocardiographic studies made by one of the authors[10] during the insulin shock treatment in 40 patients between the ages of 20 and 40 years who received between 100 to 340 units of insulin, significant QT prolongation was observed in 6 subjects. This was usually accompanied by ST depression or T wave flattening. The QT prolongation ranged between 20 and 33% above the normal predicted value and returned to normal within a few hours after the blood sugar had returned to normal.

Avitaminosis. Lengthening of the QT interval in avitaminosis has been recorded by Feil[28] and Weiss and Wilkins[68] and Gelfand and Bellet[36] in association with deficiency of vitamin B_1. This prolongation is rarely marked in degree. In this series 3 cases of "beriberi heart" demonstrated this finding. These changes were reversible in character and returned to normal as the condition improved.

Quinidine. That the QT interval may be prolonged by quinidine administration has been noted by many observers[14,59,64]. It is a rather common experience to observe this finding in patients with normal sinus rhythm who are maintained on full doses of the drug. Indeed, this is an early and significant indication of quinidine action. The prolongation parallels rather closely the degree of quinidine effect. This series comprised 8 patients with significant prolongation resulting from quinidine administration. Following cessation of quinidine administration the QT segment rapidly returned to normal.

Unknown Etiology. In 6 patients the etiology was classified as "unknown" because these patients exhibited none of the clinical or laboratory criteria which would have placed them in the groups mentioned in Table 1. Future studies may make it possible to place them in their proper categories.

Discussion. The Normal QT Interval. The QT interval of the electrocardiogram, the segment from the beginning of the Q to the end of the T wave, has been considered to be the best measure of electrical systole. This value approximates fairly well the length of mechanical systole when the QT segment presents a normal or almost normal value. When the QT segment is considerably prolonged, mechanical systole is normal or even shorter than normal. When the QT interval is abnormally short, mechanical systole is usually normal[39,40].

The QT interval at a given rate in a normal electrocardiogram has a fairly constant value. It is longer with slower rates and relatively shorter with faster rates. Bazett[7] (1920) established a formula for the calculation of electrical systole (QT): $s = K\sqrt{c}$ where s = length of systole (QT interval), c = cycle length, and K = a constant; this constant is 0.37 for men and 0.40 for women. Other investigators[4,35,41,42], basing their results on studies of a series of normals, have established formulas that give values similar to, or that deviate only slightly from, those of Bazett's.

Recently Taran and Szilagy[65] (1947), using Bazett's formula, preferred to call the K of the QT corrected for rats, the QT_c. In 80.9% of 117 normal tracings

the QT_c varied from 0.38 to 0.42 seconds[65]. The QT_c in question is compared with the predicted QT_c to determine whether it is within the normal range or prolonged. To facilitate QT segment measurement a nomogram has been prepared by several observers[38,46].

The QT and the QU Segment. In many electrocardiograms the length of the QT interval is difficult to determine because of a U wave superimposed on the terminal portion of the T wave. In other instances a prominent U wave is separated from the T wave by a very short interval. Prominent U waves were observed by one of the authors in 40% of the cases with hypopotassemia[13]. They are much more likely to occur and are of higher amplitude in the group accompanied by alkalosis. Two types of electrocardiographic alterations in these patients were observed in the QT or QU interval: 1) prolongation of the QT interval proper (this was observed in most of the cases; 2) a relatively normal, or slightly prolonged, QT interval followed by a prominent U wave (observed in a small group of cases). Nahum and Hoff[36] and other physiologists[24,26] are of the opinion that the U wave should be considered part of the electrical systole. In the presence of a prominent U wave associated with hypopotassemia it is the authors' feeling that the U wave should be considered a part of the QT segment (electrical systole) for the following reasons: 1) Consecutive cycles show prolongation of the QT segment in one cycle and a normal QT followed by a U wave in the next cycle. The QT and QU lengths in these cycles were identical. This sequence of events was observed in 4 cases. 2) Following potassium administration to a patient in whom a prominent U wave with a normal QT was present, the U wave disappeared with little change in the T wave proper. The resultant effect was similar to that observed on a prolonged QT interval[13].

From the above evidence as well as the data observed in these cases, it appears that in hypopotassemia the QT or QU interval may be used interchangeably for diagnostic purposes as a measure of electrical systole.

Causes of Lengthening of the QT Interval. The clinical conditions associated with QT prolongation are classified under 6 headings (with various subdivisions) as noted in Table 1: 1) electrolyte disturbances, 2) myocardial abnormality and/or disease, 3) conditions associated with myocardial anoxia, 4) combined factors, 5) drugs, 6) unknown etiology.

In some of these patients more than one factor was apparently operative in producing the QT segment prolongation (subdivision 4 in Table 1). The authors believe that the classification given above may be helpful in a systematic approach to the cause of these electrocardiographic changes. As knowledge of this subject increases, such a table may become more simplified.

The cardiac findings of hypocalcemia[5,17,27,41,70] and hypopotassemia[9,11,13,44,50,54,56,62,63] have been discussed in detail in recent papers and will therefore not be mentioned further in this report.

Electrocardiographic Effects of Multiple Electrolyte Alterations. In most of the clinical states associated with electrolyte imbalance, multiple electrolyte disturbances, both intracellular and extracellular, are present. The electrocardiographic effects associated with alterations in serum calcium and potassium are fairly clearcut. Abnormal values of serum magnesium have been shown experimentally and occasionally in clinical states to modify the QT segment[52]. However, alterations in this electrolyte have been little studied up to the present time. The

combination of the electrocardiographic effects of hypocalcemia and hypopotassemia has been discussed above.

In patients with fluid loss due to vomiting there is usually observed a high CO_2 blood content, hypochloremia, hypophosphatemia, occasionally hyponatremia, and frequently azotemia. The decrease in serum phosphate usually parallels the decrease in serum potassium. This has been observed by the authors in vomiting states and following treatment of diabetic acidosis. In azotemia a reciprocal relationship exists between serum phosphate and serum calcium. As far as the authors are aware, alterations in sodium, chloride and phosphates do not *per se* produce electrocardiographic alterations. However, profound alterations in these electrolytes may indirectly produce electrocardiographic changes by affecting serum potassium and, to a lesser degree, serum calcium.

Alterations in pH apparently have a considerable effect on serum potassium; alkalosis is usually associated with hypopotassemia and acidosis with hyperpotassemia.*

Darrow[21] has shown that in alkalosis accompanying vomiting states associated with normal renal function the muscle potassium varies inversely with the serum bicarbonate and the intracellular sodium varies directly with the serum bicarbonate. The administration of sodium chloride results in an increased excretion of potassium, particularly in dehydration states accompanied by hypopotassemia. The sodium ion enters the cell and tends to replace potassium.

The foregoing represent a few examples of combined electrolyte alterations. The various combinations that exist in different disease states may directly or indirectly affect the electrocardiogram.

Myocardial Disease. The cause of QT segment prolongation in patients with myocardial disease associated with hypertension and myocarditis remains obscure. In patients with coronary arteriosclerosis myocardial anoxia may be a factor. It is difficult to understand why such changes, if due to severe myocardial damage, are not observed more frequently and with more uniformity. Berliner[15] observed 24 of 54 patients with myocardial disease associated with hypertension who showed QT prolongation. Meakens[51] and Fenn[32] have also observed QT prolongation in hypertension and Feil and Katz[29] observed prolongation of mechanical systole in 1/3 of cardiac patients without failure. Fredericia[35] (1921) observed QT lengthening in patients with myocardial disease, especially those with mitral and aortic disease. He considered its presence as evidence of myocardial weakness. Cheer[18] (1930) found the QT interval to be prolonged in 155 patients with heart failure prior to treatment. Behr[8] (1934) observed QT prolongation in heart damage accompanying malignant diphtheria. Taran and Szilagyi[65] and others have reported the frequent occurrence of QT prolongation during rheumatic activity. In such cases it is probably the result of rheumatic myocarditis. The prolongation was not a function of the heart rate but was related to the severity of the disease and did not return to normal until long after other diagnostic signs gave no evidence of activity.

Myocardial Anoxia. The effects of myocardial anoxia on the QT interval are shown in Figs. 4 and 5. QT prolongation following myocardial infarction has been recorded by several authors[6,41,48]. They point out that this prolongation is more apt to occur in massive infarction. It is difficult to see,

* Mudge[53] and others have observed hypopotassemia in association with acidosis. The authors have also observed this association.

however, why QT prolongation is only occasionally observed in the presence of infarction and is frequently absent in extensive infarcts. In pulmonary embolism varying degrees of anoxia are present due to the diminished pulmonary capillary field and the right ventricular strain. Some of the most marked degrees of QT prolongation have been observed in this state. The severe grade of anoxia in dying hearts explains the marked QT prolongation observed in such patients. The effect of anoxia in producing QT segment prolongation in a patient emerging from a Stokes-Adams seizure is well illustrated in Fig. 5. Rothchild and Kissin[58] observed QT prolongation in anoxia in experimentation on the human subject. The cause for QT prolongation in the presence of anoxia has not been definitely established. Recently Fenn and Gerschman[32] have shown a loss of potassium during anoxia in nerve tissue. A similar mechanism may be operative in muscle.

Combined Factors. In certain conditions several factors may influence QT segment prolongation. In hypoglycemia produced by insulin treatment of schizophrenia the following factors may be operative:

1) Hypopotassemia. This is not nearly so marked as is observed in diabetic acidosis[1,16,37]; the serum potassium rarely falls below 3.5 to 3.7 mEq./L. Insulin action results in a shift of the potassium from the serum of the muscle and liver during the process of glycogenesis[2,31]. 2) Anoxia. It has been shown that a similarity exists between hypoglycemia and oxygen deficiency produced by inhalation of a gas mixture deficient in oxygen[20,43,45,72]. In addition, the increased work of the heart in hypoglycemia results in varying degrees of coronary insufficiency with anoxia. In avitaminosis, particularly the type associated with vitamin B_1 deficiency ("beriberi heart"), profound changes occur in the heart muscle. This has been described by Wenckebach[69] and recently by Weiss and Wilkins[68]. In a well developed case there is observed dilatation of the heart chambers, especially of the right heart, accompanied by congestive failure. Histologic study reveals hydropic degeneration of the heart muscle. In this condition the following factors may be operative in producing QT prolongation: 1) low potassium due to diminished intake, 2) myocardial disease, 3) probably anoxia due to pressure on the muscle fibers by interstitial edema, the anemia and the increased cardiac work (high output failure) which tend to produce coronary insufficiency, 4) lack of vitamins, and 5) the lack of vitamin B_1 and potassium which may disturb the normal enzymatic processes taking place in the heart muscle.

Quinidine. It has long been known that quinidine results in lengthening of the QT interval[59,64]. Indeed, this is an important manifestation of its action in patients with a normal sinus rhythm. This effect may be observed in 15 minutes following the administration of 0.8 gm. by mouth or intramuscularly. This prolongation may be quite marked in patients presenting high quinidine concentration in the plasma. In such instances evidences of its toxic effects may also be observed (Fig. 6).

Investigation of Cause of QT Prolongation. The underlying etiology of QT segment prolongation is frequently easily ascertainable. However, in some patients the cause is determined only after considerable methodical investigation. The elucidation of the underlying cause requires a careful history, clinical examination, and laboratory investigation. The following points are important: a history of fluid loss by vomiting or diarrhea, inanition, paren-

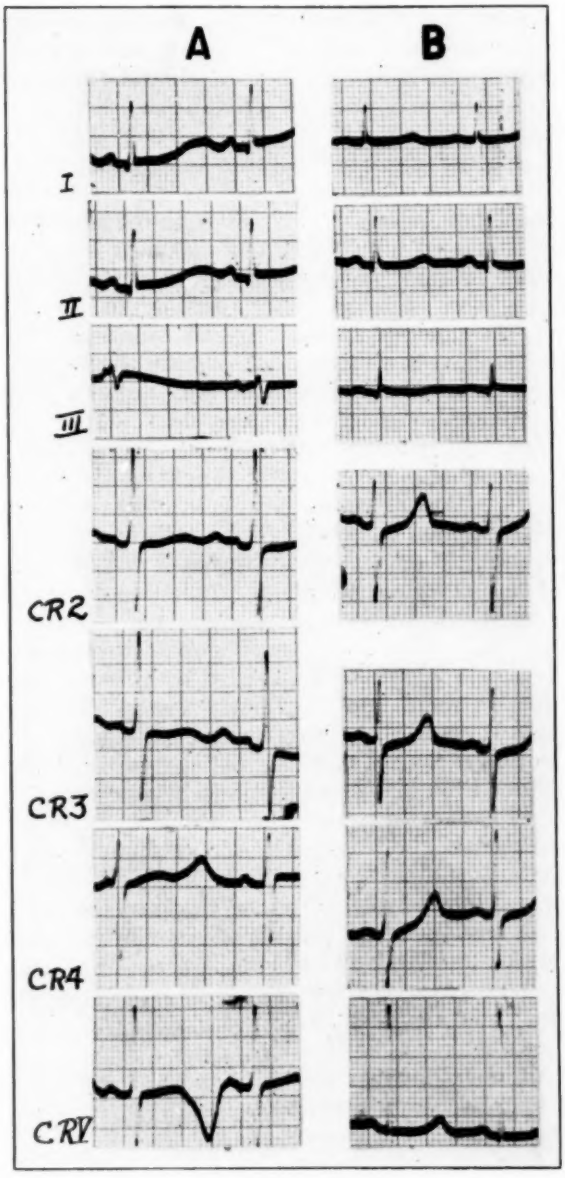

FIG. 6.—QT prolongation resulting from quinidine administration. E. B., a female, age 45, was subject to attacks of ventricular tachycardia and ventricular flutter which were treated during attacks and prophylactically with quinidine.

A. After 10 grains of quinidine had been given every 2 hours for 2 days. Note marked QT prolongation, 90% above predicted normal.

B. Four days after quinidine was stopped. Note shortening of the QT interval with upright T waves in leads I and II and in the precordial leads.

teral administration of fluid without oral administration of food, use of adrenocortical extracts, and treatment of diabetic acidosis are suggestive of hypopotassemia. The suspicion may be confirmed by the electrocardiogram, by chemical findings, and the return of the electrocardiogram to normal following the administration of potassium.

When alkalosis associated with fluid loss due to vomiting was present the following alterations were observed in the T wave and QT segment[13]: 1) ST depression of varying grades (Pattern 1), 2) normal or increased T wave amplitude with QT prolongation (Pattern III), 3) prominent U waves associated with QT or QU prolongation (Fig. 1). (Patterns IV and V). During emergence from diabetic acidosis the presence of varying types of T wave inversion accompanied by QT prolongation was the pattern most frequently encountered (Pattern II).

The presence of etiologic factors known to cause hypocalcemia and the presence of tetany suggest that this cation may be causative. Such a diagnosis may be confirmed by the electrocardiogram and estimation of serum calcium and disappearance of symptoms and alterations in the electrocardiogram following administration of this electrolyte. In the presence of hypertension, myocardial infarction and pulmonary embolism, the QT segment prolongation was observed in addition to the characteristic pattern of these states. Although the electrocardiogram is of help in raising a suspicion of the cause of the QT segment prolongation, the final diagnosis can be established only by the history and the clinical and chemical findings.

Summary. The report consists of a study of 168 patients representing QT segment prolongation due to various etiologies. The etiology of the QT prolongation was determined from the history, clinical examination, and various studies including chemical estimations of electrolytes. In the latter group return to normal of the QT interval, as well as T wave changes, was observed following the administration of the specific deficient electrolyte.

The presence of QT segment prolongation in the electrocardiogram is a sign of considerable diagnostic importance; this finding is associated with varying degrees of myocardial derangement and disease; a return to normal occurs when the myocardial abnormality is corrected.

As a result of this study the authors have classified the clinical conditions associated with QT prolongation under the following headings: 1) electrolyte disturbances, 2) myocardial abnormality and/or disease, 3) conditions associated with myocardial anoxia, 4) combined factors, 5) drugs, and 6) unknown etiology.

QT segment prolongation together with characteristic ST and T wave changes is an important diagnostic criterion of diminution in the serum calcium and potassium. The administration of these electrolytes with electrocardiographic guidance is of considerable practical importance in the treatment of these electrolyte deficiencies.

The presence of QT segment prolongation as evidence of myocardial alteration was observed in hypertension, hypoglycemia, avitaminosis, and varying types of inflammatory disease of the heart muscle. Its association with varying degrees of myocardial anoxia and quinidine administration is discussed.

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THE THROMBIN-INHIBITORY EFFECT OF CERTAIN THROMBOPLASTIN PREPARATIONS*

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The phenomenon of blood coagulation involves a complex series of reactions. Yet in assessing the over-all effect of various substances upon clotting, little attention has been paid to the possibility that a given substance might have opposite effects on the several stages of coagulation. Tissue extracts are recognized as having clot-accelerating properties. However, Mawson[4] observed that some thromboplastin preparations have slight inhibitory action on the clotting of fibrinogen by thrombin. In the experiments to be described it was shown that thromboplastin preparations from a number of sources appeared to have thrombin–inhibitory properties.

Materials and Methods. Bovine thrombin‡ was dissolved in barbital buffer and diluted to appropriate concentrations. Dried bovine fibrinogen§ (85% clottable) was dissolved in barbital buffer to a concentration of 1%. Prothrombin-deficient plasma was prepared by shaking oxalated human plasma with approximately 1/5 its volume of powdered barium sulfate and incubating at 37° C. for 10 minutes. The barium sulfate was then removed by 2 successive centrifugations. The supernatant fluid was used as a source of fibrinogen in some of the experiments. Barbital buffer was prepared from the following substances: sodium diethylbarbiturate 2.06 gm., diethylbarbituric acid 2.76 gm., sodium chloride 7.3 gm., and sufficient triple distilled water to bring the total volume to 1 liter. To facilitate solution the mixture was heated gently without boiling. The pH value of this solution was 7.5 ± 0.1. Protamine•• 1% was serially diluted with barbital buffer to the desired concentrations.

Brain thromboplastin was prepared from the acetone-extracted brain tissue of dogs and rabbits by the method of Brambel[1]. In some instances the suspensions were centrifuged at 11,000 revolutions per minute in a Servall angle centrifuge for 10 minutes to reduce the amount of particulate matter. The supernatant material was only slightly opalescent. By centrifugation the amount of brain solids in the supernate was reduced from about 50 to 10 mg. per cc. of suspension. Several of the centrifuged specimens of brain thromboplastin were dialyzed for 24 hours in 1-inch No-jax cellophane sausage casings against repeated changes of 0.85% saline solution.

Crude aqueous beef lung thromboplastin was prepared by the method of Ware and Seegers[7]. The resulting suspension was centrifuged at 11,000 rpm for 30 minutes. The sediment was homogenized in a Potter–Elvehjem type of homogenizer and resuspended in 0.85% saline solution to about ¾ the original volume of the crude material. Both the supernatant fluid and the resuspended sediment were used in the experiments.

Rabbit lung thromboplastin†† was prepared by crushing the 50 mg. tablet in 2.5 cc. of 0.85% saline solution, heating at 57° C. for 10

* This investigation was supported by a research grant from the National Institutes of Health, U. S. Public Health Service.

† Postdoctorate Fellow, U. S. Public Health Service.

‡ Obtained through the courtesy of the Upjohn Company, Kalamazoo, Michigan.

§ This material was kindly supplied by Dr. Walter H. Seegers, Department of Physiology and Pharmacology, Wayne University College of Medicine, Detroit, Mich.

•• Protamine was kindly supplied by Eli Lilly & Co., Indianapolis.

†† These commercial thromboplastin preparations (Thromboplastin-Chilcott, or rabbit lung, and Simplastin, or lung and brain solution) were kindly supplied by Dr. William T. Strauss of the Chilcott Laboratories, Division of the Maltine Company, Morris Plains, New Jersey.

minutes, and centrifuging at 1700 rpm for 4 minutes to remove the grossly particulate material. Lung and brain solution† was prepared by dissolving the contents of 1 vial in 4 cc. of distilled water.

The time for the clotting of fibrinogen by the addition of thrombin in the presence of various test substances was determined in the following manner: to 0.2 cc. of fibrinogen solution were added 0.2 cc. of buffer or of the thromboplastin preparations to be tested. These were mixed by gentle agitation and placed in a water bath at 37° C. Several minutes later 0.2 cc. of thrombin solution were added, and the time necessary for clot formation was noted. The appearance of the first fibrin threads was recorded as the end point. All determinations were repeated at least once, and the average of the readings was recorded.

One-stage prothrombin times were carried out on oxalated human plasma by the method of Quick, using the various thromboplastin preparations described. Since the lung and brain preparations contain calcium chloride, 0.1 cc. of oxalated plasma was added to 0.2 cc. of lung and brain solution, and the time necessary for clot formation was noted. All tests were carried out in duplicate at 37° C.

Calcium levels were determined by a Clark–Collip modification of the Kramer and Tisdall method.* Determinations of the pH values of the various solutions used were carried out, using a Beckman laboratory model G pH meter.

TABLE 1.—THE EFFECT OF RABBIT BRAIN THROMBOPLASTIN ON THE THROMBIN–FIBRINOGEN REACTION

Concentration of Thrombin Solution	*Clotting Times of Thrombin–Fibrinogen Mixtures to which 0.2 cc. of the Following Have Been Added:*					
	Rabbit Brain Thromboplastin					*Barbital Buffer*
	Undiluted	*1:2*	*1:5*	*1:10*	*1:50*	
u./cc.	*sec.*	*sec.*	*sec.*	*sec.*	*sec.*	*sec.*
2.0	28	26	21	21	17	18
1.5	38	33	32	32	28	26
1.0	64	51	46	42	36	33

To 0.2 cc. of fibrinogen solution were added 0.2 cc. of buffer or of the various thromboplastin dilutions noted above. Finally 0.2 cc. of thrombin solution were added to the mixture and the time necessary for clot formation was noted.

TABLE 2.—THE EFFECT OF RABBIT BRAIN THROMBOPLASTIN† ON THE CLOTTING OF PLASMA BY THROMBIN

Concentration of Thrombin Solution	*Clotting Times of Mixtures of Thrombin and Oxalated Plasma to Which 0.2 cc. of the Following Have Been Added:*					
	Rabbit Brain Thromboplastin					*Barbital Buffer (pH 7.6)*
	Undiluted (pH 7.3)	*1:2 (pH 7.5)*	*1:5 (pH 7.5)*	*1:10 (pH 7.6)*	*1:50 (pH 7.6)*	
u./cc.	*sec.*	*sec.*	*sec.*	*sec.*	*sec.*	*sec.*
5.0	22	25	—	23	23	22
2.0	77	47	38	35	31	32

To 0.2 cc. of barium sulfate-treated human plasma were added 0.2 cc. of buffer or of the various dilutions of thromboplastin as noted above. Finally 0.2 cc. of thrombin solution were added to the mixture, and the time necessary for clot formation recorded.

Results. THE EFFECT OF VARIOUS THROMBOPLASTIN PREPARATIONS ON THE THROMBIN—FIBRINOGEN REACTION. Most of the thromboplastin preparations tested showed a definite retarding influence on the conversion of fibrinogen

† See Footnote††, p. 280.

* The author is indebted to Mrs. Florence White of the Clinical Chemical Laboratory for the calcium determinations.

to fibrin by thrombin. Table 1 shows that this thrombin-inhibitory effect could be detected at a 1:10 dilution of the original rabbit brain preparation. Table 2 demonstrates that the thrombin-inhibitory phenomenon was present when plasma was substituted for fibrinogen solution. Usually the thrombin-inhibitory activity was detectable when the final concentration of thrombin was about 0.7 unit per cc. However, when more concentrated thrombin solution was used, the effect was not apparent (Table 2). Similar results were obtained when fibrinogen solution was substituted for plasma.

Studies with beef lung thromboplastin showed that the crude aqueous extract and the supernate after centrifugation had thrombin-inhibitory activity (Table 3). However, the sedimentable material lacked the thrombin-inhibitory property. The sedimentable material from brain thromboplastins likewise had little or no thrombin-inhibitory activity.

Although both dog brain and rabbit lung thromboplastin had thrombin-inhibitory activity, the lung and brain preparation lacked this property and even appeared to accelerate the thrombin–fibrinogen reaction (Table 4). It seems quite possible that the calcium content of the lung and brain preparation accounted for this accelerating effect on the reaction.

The thromboplastic activity of the various preparations as tested against human plasma did not appear to be related to the degree of thrombin-inhibitory activity. The sedimentable thromboplastin preparation of beef lung lacked thrombin-inhibitory effect and at the same time had greater thromboplastic activity than the other beef lung preparations (Table 3). On the other hand, rabbit lung thromboplastin had both more thrombin-inhibitory and thromboplastic activity than rabbit or dog brain extracts (Table 4). Thus there appeared to be no consistent relationship between thrombin-inhibitory and thromboplastic activities.

TABLE 3.—A COMPARISON OF THE THROMBIN-INHIBITORY AND THROMBOPLASTIC ACTIVITIES OF BEEF LUNG THROMBOPLASTIN

	Beef Lung Thromboplastin Preparations			*Buffer*
	A	*B*	*C*	
	sec.	*sec.*	*sec.*	*sec.*
Clotting time of thrombin-fibrinogen mixtures	54	35	25	26
One-stage prothrombin time on human plasma	34	39	23	—

A = Crude beef lung thromboplastin suspension.

B = Supernatant fluid after centrifugation of the crude extract at 11,000 rpm for 30 minutes.

C = Sediment obtained after centrifugation. This material was homogenized and reconstituted with 0.85 % saline solution to $\frac{2}{3}$ the original volume of the crude preparation.

To 0.2 cc. of fibrinogen solution were added 0.2 cc. of buffer or of the various thromboplastin preparations noted above. Finally 0.2 cc. of a thrombin solution containing 2.0 units per cc. were added to the mixture and the time necessary for clot formation noted. One-stage prothrombin times were determined on normal human plasma using the various thromboplastin preparations described.

NATURE OF THE THROMBIN-INHIBITORY ACTIVITY OF THROMBOPLASTIN PREPARATIONS. Temperature, pH, salt concentration (in particular calcium and oxalate ions), and fibrinogen con-

centration and reactivity influence the thrombin–fibrinogen reaction appreciably[5]. Although it appears obvious that most of these were controlled within each of the above experiments, a few factors deserve further consideration.

It is well known that the pH of the reaction mixture may influence the thrombin–fibrinogen reaction with maximal thrombin activity present in the range of pH 6 to 8[5]. Most of the thromboplastin preparations had slightly lower pH values than that of the barbital buffer even when the latter was used as a diluent in the preparation of the thromboplastin from the dried state (Table 2). However, this difference was slight and well within the range of maximal activity of thrombin. Experiments in which pH values were controlled demonstrated that the thrombin-inhibitory activity could not be accounted for by differences in pH value.

The calcium ion concentration is known to influence the rate of the thrombin–fibrinogen reaction[5]. However, this effect is rather slight over wide ranges of calcium concentration. Both the brain thromboplastin suspensions and the buffer solution had calcium levels of less than 0.6 mg. per 100 cc. This concentration is well below the level which materially influences the thrombin–fibrinogen reaction[5].

Oxalate solutions may exert a profound retarding effect on the conversion of fibrinogen to fibrin by thrombin[5]. Since 0.2 cc. of 1/10 molar sodium oxalate solution was added to 10 cc. of brain thromboplastin suspensions during their preparation, this factor deserves further consideration. Thromboplastin prepared without the addition of oxalate solution was likewise thrombin-inhibitory. When 0.2 cc. of a 1/10 molar solution of sodium oxalate was added to 10 cc. of barbital buffer and the resulting solution was added to a thrombin–fibrinogen mixture, the thrombin–fibrinogen reaction was not retarded.

The thrombin-inhibitory effect remained after thromboplastin suspensions were heated in a water bath at 100° C. for 30 minutes, dialyzed against frequent changes of 0.85% saline solution, or repeatedly extracted with

TABLE 4.—A COMPARISON OF THE THROMBIN-INHIBITORY AND THROMBOPLASTIC ACTIVITIES OF VARIOUS THROMBOPLASTIN PREPARATIONS

EXPERIMENT 1

	Thromboplastin Preparations			*Barbital Buffer*
	Rabbit Brain	*Dog Brain*	*Rabbit Lung*	
	sec.	*sec.*	*sec.*	*sec.*
Clotting time of thrombin-fibrinogen mixtures	30	27	34	21
One-stage prothrombin time on human plasma	16	26	14	—

EXPERIMENT 2

	Thromboplastin Preparations		*Barbital Buffer*
	Dog Brain	*Lung and Brain*	
	sec.	*sec.*	*sec.*
Clotting time of thrombin-fibrinogen mixtures	29	20	24
One-stage prothrombin time on human plasma	30	20	—

The methods used here were described in the previous tables and in the section on methods. Thrombin solution had a concentration of 2.0 units per cc.

ether. Freezing and subsequent thawing of thromboplastin did not alter this property. Seitz filtration was accompanied by a complete loss of thrombin-inhibitory as well as thromboplastic activity.

Incubation of thrombin or fibrinogen with thromboplastin at 37° C. for 20 minutes did not lead to greater retardation of the thrombin–fibrinogen reaction than was observed prior to incubation. Therefore, it seems likely that neither did the thromboplastin preparations progressively destroy thrombin nor did they greatly alter the reactivity of fibrinogen. It appears more probable that the addition of protamine significantly counteract the thrombin-inhibitory activity of thromboplastin preparations. Thus no evidence was found that heparin or a heparin-like compound was involved. Protamine alone reduced the thrombin–fibrinogen clotting time when the former was present in relatively great concentration, an observation previously made by Ferguson[3]. Similar results were obtained when plasma was substituted for fibrinogen solution and when toluidine blue† was used as the antiheparin compound.

Discussion. The rate at which fibrinogen is clotted by thrombin is subject to the influence of a number of factors including temperature, pH, ionic concentrations, and fibrinogen concentration and reactivity. In addition it was found that certain thromboplastin preparations had thrombin-inhibitory activity. Owren[5] was unable to demonstrate any influence of thromboplastin on the thrombin–fibrinogen reaction with the concentration of reagents he used. However, the concentration of thrombin he used was greater than that in the experiments recorded here. With more concentrated thrombin solutions no thrombin-inhibitory effect could be demonstrated.

TABLE 5. THE EFFECT OF PROTAMINE SULFATE ON THE THROMBIN-INHIBITORY ACTIVITY OF RABBIT BRAIN THROMBOPLASTIN

Clotting Time of Thrombin–Fibrinogen Mixtures to Which 0.2 cc. of the Following Have Been Added:									
Thromboplastin Containing the Following Amounts of Protamine (mg. per cc.)					*Buffer Containing the Following Amounts of Protamine (mg. per cc.)*				
0.1	0.05	0.01	0.005	0	0.1	0.05	0.01	0.005	0
sec.	*sec.*	*sec.*	*sec.*	*sec.*	*sec.*	*sec.*	*sec.*	*sec.*	*sec.*
27	27	28	27	30	9	13	22	22	22

The thrombin–fibrinogen clotting times were determined as outlined in the previous tables and in the section on methods. The thrombin solution had a concentration of 2.0 units per cc.

thromboplastin suspensions interfered with the mechanics of the thrombin–fibrinogen reaction in some manner as yet unexplained.

PROTAMINE TITRATIONS. Studies were carried out to determine if heparin or a heparin-like compound could account for the thrombin-inhibitory effect of thromboplastin preparations. The addition of 0.2 cc. of barbital buffer containing 0.1 unit of heparin* per cc. to the thrombin–fibrinogen mixture tripled the clotting time. This finding suggested that heparin co-factor[6] was present in the mixture, and that heparin could exert an effect in this clotting system. Table 5 shows that in no instance did

* Heparin sodium was kindly supplied by the Upjohn Company, Kalamazoo, Michigan.
† Toluidine blue, special batch No. 2, serial E-1204, Abbott Laboratories.

The precise nature of the thrombin-inhibitory activity of some thromboplastin preparations remains unknown. Whether this is due to thromboplastin itself or some other substance present in the preparation is not known. The finding that the sedimentable material of thromboplastin suspensions was not thrombin-inhibitory but still was potently thromboplastic suggests that the thrombin-inhibitory property is not due to thromboplastin itself. The substance which determines the thrombin-inhibitory activity appears to be non-dialyzable, heat-stable (100° C. for 30 minutes), not extractable with ether, and not filterable through a Seitz filter. This suggests that the responsible substance may be a large molecule.

The finding that some thromboplastin preparations have thrombin-inhibitory activity may be of significance in relation to the reliability of certain laboratory tests for the estimation of prothrombin concentration. This thrombin-inhibitory effect may play a rôle in the discrepancies noted in prothrombin estimations using different thromboplastins[2].

Summary. 1. Certain thromboplastin preparations were found to have thrombin-inhibitory activity. Some observations on the nature of this activity are given.

2. When the concentration of the thrombin used was increased sufficiently, the thrombin-inhibitory effect was not detectable.

3. The possible relationship of this thrombin-inhibitory activity to the reliability of certain laboratory tests for the estimation of prothrombin concentration is mentioned.

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STUDIES ON CHLORAMPHENICOL IN THE TREATMENT OF TYPHOID FEVER*

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WHILE typhoid fever is today practically unknown in most progressive countries, it is still endemic in the Philippines. There are several important reasons to account for this unfortunate situation, but, of the most pertinent, we may mention the lack of a fully developed system of public sanitation, our relatively lower standards of living, the general poverty of the masses, and the undeveloped natural resources. All these conditions have been made much worse by the vicissitudes of the last war. Present economic difficulties make the correction of these deficiencies a program for the future.

With the above unfavorable picture in mind, it is but natural that those who are interested in public health work welcome with enthusiasm the advent of chloramphenicol, for it bids fair to help solve some of the problems in typhoid fever. The writers, therefore, have engaged in a series of studies on chloramphenicol (chloromycetin) therapy, in the hope that, if their results are favorable, the co-operation of others in the medical profession may be invited to undertake serious studies of the application of this important antibiotic in cases of typhoid fever in the Islands.

Method. Fifty-five cases of typhoid fever, selected for their approximately equal degree of severity, and because of an almost identical average duration of illness before treatment was started, were used in this study.

Fifty of these cases (90.90%) came from the charity wards of the San Lazaro Hospital, Manila, and the remaining five (9.10%) were private patients of the senior author. Twenty-four patients (43.27%) were males and 31 (56.73%) were females. The age incidence is as follows:

TABLE 1.—AGE INCIDENCE IN 55 CASES OF TYPHOID FEVER

Ages, years	*Cases*
11–15	8
16–20	13
21–25	8
26–30	12
31–35	7
36–40	6
41–45	0
46–50	1
TOTAL	55

Clinical diagnosis was in every case confirmed by blood cultures positive for *S. typhosa*. Thirty-one cases (including the 5 private patients), or 56.73%, were subjected to chloramphenicol therapy, while the remaining 24 (43.27%) were used as control cases and treated symptomatically with the usual well-known supportive measures.

Following bacteriological confirmation of the diagnosis, treatment was begun by giving chloramphenicol orally in initial doses vary-

* Partially supported from funds of the United States Public Health Service, Philippines Public Health Rehabilitation Programs, Brig. Gen. Howard F. Smith in charge.

ing from 1 to 2.5 gm., estimated on the approximate basis of body weight, and followed later by doses of 0.25 gm., repeated every 2, 3, or 4 hours during the febrile period. Upon subsidence of the temperature, the dose was gradually reduced by lengthening the time intervals of the administration for an average of approximately 1 week, counting from the last day of the fever (afebrile period).

Results. In our chloramphenicol-treated cases, the average number of days of the fever from the onset of treatment (febrile period) was 4.48 (the extremes being 2 and 8 days), and during this period, an average dosage of 12.07 gm. of chloramphenicol was given. However, the actual febrile period, that is, the number of days with fever during the whole course of the ailment, was much longer, as all these patients had had elevation of temperature for many days before their admission to the hospital. This total average duration of the fever from onset of the disease until subsidence of the temperature was 16.91 days, while the average total number of days without fever, but still under treatment, was 7.04, during which period an average dosage of 9.94 gm. of chloramphenicol was administered. A total dosage of 22.01 gm. was given during the febrile and afebrile periods of 11.52 days (Table 2).

Twenty-three cases (including the 5 private cases), or 74.19%, of the total of 31 cases treated with chloramphenicol made complete recovery. Eight cases (25.81%) ended fatally, death occurring during the febrile period, that is, within an average of 2.12 days from the beginning of the treatment. If to this short period of fever we add the number of febrile days before admission, the average total number of days with fever in these fatal cases was 17. Unlike the treated cases with recovery, none of the fatal cases received treatment after the febrile period, since none of them reached an afebrile period (Table 3).

In the control cases, the average duration of fever was 36.75 days, counted from the day of the onset of the disease, as compared to 16.91 days in the treated cases (Table 4). There is, therefore, a difference of 19.84 days in favor of chloramphenicol therapy. In the treated cases that ended fatally the average duration of the fever from the onset of the illness to death was 17 days. The average duration of fever under chloramphenicol treatment was

TABLE 2.—CHLORAMPHENICOL TREATMENT SHOWING AVERAGE AMOUNT IN GRAMS GIVEN TO 31 CASES OF TYPHOID FEVER WITH POSITIVE BLOOD CULTURES (SERIES 1949)

		Average Amount in Gm. of Chloramphenicol Given Each Case		
Results	*Number of Cases*	*During Febrile Period*	*During Afebrile Period*	*Total*
Recovered	23	12.07*	9.94†	22.01**
Died	8	8.18††	—	8.18
TOTAL	31			

* Amount given during febrile period of 4.48 days.
† Amount given during afebrile period of 7.04 days.
** Amount given during febrile and afebrile period of 11.52 days.
†† Amount given during febrile period of 2.12 days before death.

4.48 days for cases that recovered, and 2.12 days for those that ended fatally (Table 3).

In regard to fatality rates, 8 patients, or 25.81% of the 31 treated cases, died. In the control group of 24 cases, there were 12 deaths, or a 50% mortality. In other words, the fatality rate in the treated group was ½ that in the controls. If one is inclined to regard these fatality rates as being unduly high, it must be kept in mind that all these cases were selected on the basis of their severity (Table 4).

In chloramphenicol-treated cases, symptoms such as headache and chilliness gradually subsided with the fever, and the pulse also improved. In 6 of these, delirium and mental dullness were quite marked before the administration of chloramphenicol, and the relation of the time of their disappearance to duration and dosage is shown in Table 5.

TABLE 3.—RESULTS OF CHLORAMPHENICOL TREATMENT IN 31 CASES OF TYPHOID FEVER WITH POSITIVE BLOOD CULTURE SHOWING AVERAGE DURATION OF FEVER BEFORE AND DURING TREATMENT, AND ENTIRE FEBRILE COURSE IN DAYS (SERIES 1949)

Results	*Number of Cases*	*Rate %*	*Days with Fever before Administration of Chloramphenicol*	*Days with Fever during Administration of Chloramphenicol*	*Entire Course of Fever in Days*
Recovered	23	74.19	12.43	4.48*	16.91
Died	8	25.81	14.88	2.12†	17.00
TOTAL	31	100.00			

* 12.07 gm. were given during this febrile period.
† 8.18 gm. were given during this febrile period before death.

TABLE 4.—RESULTS OF CHLORAMPHENICOL TREATMENT OF 31 CASES OF TYPHOID FEVER WITH POSITIVE BLOOD CULTURE COMPARED WITH RESULTS IN 24 CONTROL CASES WITH POSITIVE BLOOD CULTURE (SERIES 1949)

	Cases with Chloramphenicol Treatment			*Control Cases (Routine Treatment without Chloramphenicol)*		
Results	*Number of Cases*	*Rate %*	*Entire Course of Fever in Days*	*Number of Cases*	*Rate %*	*Entire Course of Fever in Days*
Recovered	23	74.19	16.91	12	50.0	36.75*
Died	8	25.81	17.00	12	50.0	24.16†
TOTAL	31	100.00		24	100.00	

* These 12 control cases had an average duration of fever of 12.01 days before admission to hospital and 24.66 days of fever inside hospital, giving a total of 36.75 days.
† These 12 control cases had an average duration of fever of 13.58 days before admission to hospital and 10.58 days of fever inside hospital before death, giving a total of 24.16 days.

TABLE 5.—RELATION OF MENTAL SYMPTOMS TO DOSAGE

Cases		*Days after Start of Treatment*	*Amount Given, gm.*
1	Adm. No. 1581–49	1	5.50
1	Adm. No. 891–49	3	10.25
2	Adm. No. 3895–49 & 9401–49	4	13.00
1	Adm. No. 5799–49	6	10.50
1	Adm. No. 7472–49	8	16.25

Sweating, moderate to severe in amount, was observed in 3 cases of the treated group. The manner of disappearance of this symptom in relation to duration and dosage was approximately as follows:

In the 1st case, the sweating started profusely 1 day after the treatment was begun. Starting with an initial dose of 2.5 gm., a total of 5.5 gm. of chloramphenicol was administered through the 1st day. The amount of the chloramphenicol was reduced to 3 gm. on the 2nd day; to 1.5 gm. on the 3rd, 4th, and 5th days; and to 1 gm. on the 6th, 7th, and 8th days, with cessation on the 9th day. The sweating gradually lessened to a slight amount by the 8th day, though there was a slight persistence until the 29th day. The fever, ranging from 38 to 40° C., disappeared after 2 days of treatment.

In the 2nd case, the sweating was observed in moderate amount on the 2nd day after treatment was started; it gradually lessened in quantity and stopped altogether on the 7th day. Chloramphenicol was started with an initial dose of 1.5 gm., a total of 3 gm. being given by the end of the 1st day. The dosage was then reduced to 1.5 gm. daily until the 12th day. The fever ranged from 38.4 to 40°C. and disappeared after the 4th day of treatment.

In the 3rd case, the sweating first appeared in moderate amount on the 4th day of treatment after 9.4 gm. of chloramphenicol had been received, and it gradually lessened and completely disappeared at the end of the 6th day. The antibiotic was reduced to 2.5 gm. on the 5th day and to 1.5 gm. daily from the 6th to the 15th days. Fever (with the temperature ranging from 38 to 39.8° C.) disappeared after 4 days of treatment.

LABORATORY EXAMINATION. Cultures were made from the blood, urine, and feces on all the charity cases both in the treated and control groups (31 treated cases and 24 controls). In all these 55 cases, the blood culture was positive for S. *typhosa* before treatment was started.

Blood cultures were repeated every 2 days during chloramphenicol treatment in the febrile period and every 4 days during the afebrile period. From the 18 charity patients who were treated with chloramphenicol and recovered, 29 blood, 29 feces, and 20 urine cultures were made during the febrile period of treatment, with uniformly negative results for S. *typhosa*.

During the afebrile period and while the patients were still under antibiotic treatment, repeated cultures were again made from these 18 patients. The 34 blood cultures were negative for S. *typhosa*, and 23 of 24 feces cultures and 31 of 32 urine cultures were also negative.

After discontinuance of the chloramphenicol treatment and subsidence of fever, repeated cultures were again made from these 18 cases (108 from the blood, 108 from the feces, and 86 from the urine); all were negative for S. *typhosa*. These patients were kept in the hospital for an average afebrile period of 48.22 days following therapy.

For obvious economic reasons, laboratory tests could not be made frequently in the 5 private cases. Moreover, because of lack of proper facilities blood levels of chloramphenicol could not be determined in any of the cases.

COMPLICATIONS. In the treated cases, the two principal complications noted were 1 instance of intestinal hemorrhage and 1 of perforation of the vermiform appendix.

The patient who hemorrhaged was treated on the 11th day of the disease

and had a temperature of 40° C. with a pulse of 118 per minute; he had marked tympanism and complained of severe headache. Thirty hours after start of therapy, after he had received 5.75 gm. of chloramphenicol, the pulse improved to 85 per minute and the fever came down to 38° C. However, the temperature rose again to 39.4° C. several hours later, the pulse rising to 120 per minute. Forty-four hours after the initial treatment, and after having received a total of 7.75 gm. of chloramphenicol, the patient became unconscious, developed cold clammy perspiration, and died 5 hours later. Necropsy revealed intestinal hemorrhage, typhoid enteritis, ulcerations in the lower ileum, and hypostatic congestion of the lungs.

The patient who developed perforation of the vermiform appendix was treated on the 21st day of the disease and the temperature became normal after administration for 3 days of chloramphenicol. Three days after subsidence of the temperature, and while still under antibiotic therapy, this patient showed symptoms and signs of peritonitis. On laparatomy, a perforated vermiform appendix was found, the perforation occurring in one of the lymph nodules. Chloramphenicol was continued after the operation, and by the end of the 6th day, a total of 7.75 gm. had been administered. The patient died 10 days after his laparatomy. Necropsy was refused by the family.

In the group of control cases, the most important complication observed was intestinal hemorrhage. It occurred in 8 patients, 6 of whom died. The bleeding was the most severe in the 6 fatal cases. Food was stopped immediately and venoclysis of 5% dextrose in normal saline solution was given instead, and other supportive remedies were prescribed in addition. One of the 2 patients who recovered received a transfusion of 250 cc. of fresh blood. For lack of blood donors only blood plasma (250 to 350 cc.) was given in the 6 fatal cases.

Relapses. In the group of 23 patients who were treated and recovered, 7 relapsed, 5 having positive blood cultures during the relapse. In 6 of these 7 cases, the relapse occurred on an average of 10.66 days after the last administration of the chloramphenicol. In the 7th case, however, the relapse took place after the 3rd day of the afebrile period but with the patient still under treatment (Case Adm. No. 6316—49). This patient had been receiving chloramphenicol in doses of 0.25 gm. every 4 hours so that by the end of the 3rd day when the relapse occurred, the patient had been given a total of 4.5 gm. of the drug. It was unfortunate that because of the limited supply of the antibiotic chloramphenicol could not be given to these patients during their relapse.

Smadel, Woodward, and Bailey[1] reported relapse in 7 cases out of 13. In this group, the initial course of the drug was given for 8 days or less, the average duration of the therapy being 6.9 days. No relapses were reported in 2 other groups wherein the average amount of the drug given was larger and was given over longer periods. These writers conclude, therefore, that relapses may be avoided if the drug is given in adequate amounts and for periods longer than 8 days.

Of the 12 cases in our control group who recovered, 5 relapsed (41.66%). The relapse occurred 9.4 days on an average after the temperature had become normal.

Mortality. Of the 31 patients treated with chloramphenicol, 8 died (25.81%). In the control group of 24 patients, 12 or 50% died, a difference of 24.2% in favor of the treated cases. If to the reader the fatality rates appear to be unduly high, it should be

remembered that these cases were uniformly in very serious condition with severe toxemia. In only 3 out of the 8 fatal cases in the treated group could permission for autopsy be obtained. Of the 12 control cases resulting fatally, autopsy was performed in 8. The findings were uniformly those of typhoid pathology with organisms recovered from the intestines and spleens.

Discussion. The outstanding effect of chloramphenicol treatment in our study was the marked reduction in the course of the fever, the average duration of fever in the treated group being 16.91 days, while in the control group, the average was 36.75 days, a difference of 19.84 days in favor of chloramphenicol treatment (Table 4).

In the studies conducted by Woodward[3] *et al.*, of 10 cases treated with chloramphenicol, the mean duration of the fever in all cases prior to treatment was 9.5 days. In the present group of 23 cases treated with the antibiotic, the mean pretreatment duration of fever was 12.43 days. The mean duration of the fever after treatment was started was 3.5 days in the former series and 4.48 days in the treated group (Table 3).

In 1949, Woodward[2] also reported another study on 21 cases, the average total amount of chloramphenicol given being 22.7 gm. per patient over a period of 9.1 days. To the present group of 23 patients treated with chloramphenicol who recovered, an average total of 22.01 gm. of the antibiotic was given over an average period of 11.52 days (Table 2).

In their series of 10 cases treated with chloramphenicol Woodward[3] and co-workers reported 2 cases of serious complications (1 of intestinal bleeding and 1 of intestinal perforation), both occurring during the afebrile period and with recovery in both. In the present group of 31 treated cases, 2 cases had similar complications as noted previously.

In 1949 Woodward[2] reported the occurrence during the afebrile period of 2 instances of intestinal hemorrhage and of intestinal perforation in a group of 21 cases; all 3 recovered.

In 8 control cases of Woodward *et al.*[3], 1 died. The average duration of the febrile period in their recovered cases was 35 days. In the control group of 24 patients in the present series, 12 died, and the average number of febrile days in the recovered cases was 36.75 (Table 4).

In the fatal cases of the treated group, the duration of the fever from onset of treatment to death was 2.12 days, and the average duration of fever before treatment was begun was 14.88 days. An average amount of 8.18 gm. of antibiotic was given during the period of 2.12 days of treatment (Table 3). The duration of the fever of the control group was 10.58 days before death, and the average duration of the fever before admission to the hospital was 13.58 days (Table 4). How can the great difference in the duration of the fever in these two groups be accounted for? Before this question can be answered, it must be emphasized again that all these cases were severe, especially, of course, the cases that terminated fatally, and this was true in both the control and the treated groups. One can only wonder whether the chloramphenicol in such severe cases might not have hastened the fatal ending. Although Woodward[2] stated that "there are no reports up to the present time of toxic manifestations resulting from oral administration of chloromycetin," still we keep asking ourselves whether, in very severe cases, this antibiotic is a hastening factor in causing death by increasing the endotoxins liberated in the blood, result-

ing from the destruction of S. *typhosa*. These results indicate that this antibiotic may be contraindicated in very severe toxic cases of typhoid fever.

Conclusions. Chloramphenicol therapy is decidedly helpful in the treatment of typhoid fever. It reduces markedly the febrile period and lowers decidedly the fatality rate, while ameliorating the other disagreeable general symptoms accompanying the fever. In the most severely toxic cases, however, the administration of chloramphenicol seems to hasten the onset of death.

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THE RECOVERY OF VIRUS FROM REGIONAL LYMPH NODES OF FATAL HUMAN CASES OF POLIOMYELITIS*

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PERIODICALLY, during the past 40 years, poliomyelitis virus has been found in regional lymph nodes of human beings who have succumbed to this disease. The efforts made to detect poliomyelitis virus in lymphatic tissues have not been many, and the number of positive tests have not been consistent enough to deserve more than passing mention. Nevertheless, a review of the published studies on the subject indicates that although poliomyelitis virus can be found only irregularly in regional lymph nodes, its presence there has been frequent enough to stimulate interest in regard to several points. Questions raised are: Is the virus present in lymph nodes often enough that its presence there must be regarded as a significant landmark in pathogenesis? If it is important in pathogenesis, what are the portals used in the entry of virus into regional lymph nodes?

The authors have repeated some of the earlier work[3,9,13,15] in order to determine the presence of virus in regional lymph nodes of human beings who have died of poliomyelitis. As others had found previously, poliomyelitis virus was found in lymphatic tissues. In this report observations and results are reported and discussed in regard to certain aspects of the pathogenesis of human poliomyelitis.

Materials and Methods. TISSUES. Necropsies performed on 9 patients were completed within a period of 2 to 10 hours after death (Table 1). Sterile techniques were followed. A midline body incision was made; the skin and subcutaneous fat were dissected far enough to expose the right and left axillary and inguinal areas. The lymph nodes in each of these quadrants were visualized and samples containing lymph nodes and adipose tissue were dissected free. Separate sterile instruments were used in the removal of each group of regional lymph nodes to sterile waxed cardboard containers. After these nodes had been obtained, the peritoneal cavity was opened. Mesenteric lymph nodes were removed first; then a piece of pancreas (4 to 8 gm.) was obtained before any other examination was made. Sterile instruments were used also in the collection of these tissues.

It was not possible to open the calvarium with sterile instruments. An effort, which was usually satisfactory, was made to keep the dura mater intact. The dura was opened with sterile scissors. The brain and the upper cervical segment of the spinal cord were removed. Segments of midbrain, medulla, and cervical cord were placed in sterile containers. At the end of each necropsy, all tissues were stored at −70° C. until they were prepared later for inoculation into monkeys.

PREPARATION OF TISSUE EXTRACTS. Each group of regional lymph nodes was prepared in the following way: The nodes were dissected free of surrounding adipose tissue. Samples ranged from 0.2 to 2.8 gm. in weight

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TABLE 1.—DATA CONCERNING FATAL ATTACKS OF POLIOMYELITIS IN 9 HUMAN BEINGS

Name	*Age (yr.)*	*Sex*	*Color*	*Date of Onset*	*Type of Clinical Illness*	*Date of Death*	*Postmortem Hours after Death*	*Findings at Necropsy other than CNS*	*CNS Lesions of Poliomyelitis*	*Poliomyelitis Virus in CNS*
C. Cara	2	F	W	8/28/49	Spinal Bulbar	9/2/49(5)*	8.0	Bronchopneumonia	+	+
V. Eber	36	M	W	7/15/49	Spinal Bulbar	7/23/49(8)	7.0	Bronchopneumonia Mesenteric lymphadenopathy	+	+
L. Henk	6	M	W	8/27/49	Spinal Bulbar	8/31/49(4)	2.5	Pulmonary congestion	+	+
E. Jeff	2	M	W	8/19/49	Bulbar	8/22/49(3)	1.5	Interstitial pneumonitis	+	+
V. Jell	11	M	W	8/17/49	Bulbar	8/21/49(4)	4.5	Bronchopneumonia Acute myocarditis	+	+
H. Mab	19	M	W	9/24/49	Bulbar	9/26/49(2)	8.5	None	+	+
D. McDon	12	F	W	9/2/49	Spinal Bulbar	9/7/49(5)	1.5	Bronchopneumonia Acute glomerulitis	+	+
H. Milh	28	F	W	9/1/49	Bulbar	9/6/49(5)	2.0	Bronchopneumonia Focal myocarditis	+	+
J. McKin	5	M	W	10/6/50	Bulbar	10/10/50(4)	2.0	None	+	+

* Figures in parentheses: elapsed time in days from onset of illness until death.

Lymph nodes were washed in 3 changes of sterile distilled water (25 cc.). They were then triturated in a mortar with pestle, using alundum as abrasive. Distilled water was used to make a final dilution of 1:10. After emulsification was completed, the extract was centrifuged (2000 revolutions per minute for 10 minutes) and the supernatant milky fluid was decanted for use in the tests. With the exception of tissues from one patient, (V. Jell), all were bacteria free following inoculation on blood agar plates and in thioglycollate broth. All the lymph node extracts for V. Jell contained gram-negative bacilli. These were removed by further centrifugation in a Swedish angle centrifuge (5000 rpm for 30 minutes). Ten percent emulsions of central nervous system and pancreatic tissues were prepared also in distilled water.

TESTS MADE FOR THE PRESENCE OF POLIOMYELITIS VIRUS. Rhesus (*M. mulatta*) monkeys were used in the tests. The majority of the monkeys had been used previously in tests made during a program of typing of strains of poliomyelitis viruses. The selection of these monkeys was made according to the following criteria: use in a) titration experiments where the PD_{50} was beyond the dilution used as estimated in a preliminary titration, and b) in serum-neutralization tests in which all monkeys had experienced unequivocal clinical protection. Less than half the monkeys in any 1 of the 2 groups were selected for use in the current study; the remaining monkeys in these two groups were sacrificed and showed no evidence of having experienced non-paralytic poliomyelitis. In a number of tests, including repeat tests of extracts found earlier to be either positive or negative, new monkeys were used.

Each monkey received 0.8 cc. of inoculum intracerebrally in the region of the thalami (0.4 cc. on each side). Following inoculation monkeys were observed daily for 30 days, unless, as is indicated in the protocols, they were sacrificed earlier. In the first tests, following use of a new diet, scurvy occurred in some of the monkeys and pseudo-paralyses distorted the clinical picture. Monkeys were sacrificed at the time of appearance of paralyses. Animals surviving without clinical evidence of poliomyelitis were sacrificed at the end of the 30-day observation period. Segments of midbrain, medulla, and cervical and lumbar segments of spinal cord were examined histologically for the lesions of poliomyelitis.

Materials were obtained also from paralyzed animals for establishment of the strain in new animals.

Results. POLIOMYELITIS VIRUS IN REGIONAL LYMPH NODES. Poliomyelitis virus was found in regional lymph nodes obtained from 6 of the 9 individuals studied. The positive tests were distributed as follows: right axillary lymph nodes, positive in 2 individuals; left axillary lymph nodes, positive in 3; right inguinal lymph nodes, positive in 2; and left inguinal lymph nodes, positive in 2. In 1 instance (J. McKin) the axillary lymph nodes were pooled; the inguinal lymph nodes were pooled also. Poliomyelitis virus was detected in axillary but not in inguinal nodes obtained from this boy. In summary, poliomyelitis virus was detected in the axillary lymph nodes of 6, and in the inguinal nodes of 4, of the 9 individuals studied. In contrast to these peripheral lymph nodes, poliomyelitis virus was found only once in mesenteric lymph nodes. The results of these tests appear in Table 2.

The detection of virus in various regional lymph nodes was erratic. Solitary isolations were made from axillary nodes of either the right or left side in 5 patients. In only 1 of the 4 individuals whose inguinal nodes were positive was virus detected bilaterally. In 4 individuals, poliomyelitis virus was found in both axillary and inguinal nodes. Demonstrable virus was not found in lymph nodes obtained from 2 patients (Eber and H. Mab). There was no correlation between the presence of virus and the age of the patient, duration of illness, or size of the lymph node sample. All of the patients had experienced a brief and rapidly fatal illness. The 2 patients whose nodes were negative were young adults (Table 1). The time elapsing between death and necropsy was longest (8 hours) in these 2 individuals. In view of the small number of patients included in the study, further discussion in regard to significant factors influenc-

TABLE 2.—RESULTS OF TESTS MADE TO DETECT VIRUS IN CNS, REGIONAL LYMPH NODES, AND PANCREAS OF HUMAN BEINGS WHO DIED WITH POLIOMYELITIS

	Tests Made in Rhesus Monkeys; Results in Respect to Tissues Tested															
	CNS		*R. Axillary LN*		*L. Axillary LN*		*R. Inguinal LN*		*L. Inguinal LN*		*Mesenteric LN*		*Pancreas*	
Patient														
C. Cara	1812†† (P9)	+	1851 (P11)	+	1826	○	2107 (NP)	⊕	1850 (P18)	+	2047	○	1843 (K20)	○
					1866	○								
	*1902 (P8)	+	1827	○	*2675	○			1852	○	2048 (K6)	○	*2629	○
					*2676	○								
V. Eber	1669 (P15)	+	2080	○	2076	○	2069	○	2081	○	2196	○	2197	○
			2090	○	2068	○	2079	○	2092	○	2252	○	2234	○
L. Henk	*2625 (P10)	+	lost		2045 (P10)	+	1983	○	2025	○	1956	○	2044 (K19)	○
	*2626 (P18)	+			2050	○	1984 (P17)	+	2036 (D8)	○	1982 (K19)	○	2052	○
E. Jeff	1485 (P8)	+	1539 (D4)	○	1537 (K25)	○	1553 (K23)	○	1549 (K11)	○	1547 (D4)	○	2195	○
	1494 (P9)	+	1564 (K18)	○	1540 (P12)	+	1556	○	1571 (K19)	○	1552 (K21)	○	2243	○
V. Jell	*899 (P9)	+	2097	⊕	2190	○	2191	○	2193	○	1987 (K23)	○	lost	
			2121	○										
			*2627	○	2236 (K21)	○	2238	○	2240	○	1995	○		
			*2628	○										
H. Mab	1462 (P10)	+	1713 (K22)	○	1717	○	1788 (K12)	○	1814 (K13)	○	1512 (D8)	○	1824	○
	1531 (P8)	+	1739 (K13)	○	1740 (D11)	○	1811 (K24)	○	1815 (D13)	○	1771 (K24)	○	1863 (D9)	○
D. McDon	*896 (P9)	+	2111 (NP)	+	2194	○	1927	○	1928	○	lost		2046	○
			2119 (P19)	+			1936 (P18)	+						
			*2673	○	2241	○	*2671	○	1937	○			2049 (K6)	○
			*2674 (P15)	+			*2672	○						
H. Milh	1659 (P7)	+	1718 (K18)	○	1646 (P6)	+	1647 (K21)	○	1668 (K7)	○	1728 (D4)	○	1729	○
					1662 (P16)	+								
	1665	○	1726	○	*2669†	○	1667 (K21)	○	1686 (P8)	+	1737 (K21)	○	*2630	○
					*2670	○								
J. McKin	2305 (P9)	+	*2617 (P8)			+	*2619			○	*2633	○	*2623	○
	2382 (P6)	+	*2618 (P10)			+	*2620			○	*2634 (P11)	+	*2624	○
Score	9/9		6/9				4/9				1/8		0/8	

+ = positive test; lesions observed which were histologically typical of poliomyelitis.
P9 = paralyzed on 9th day.
NP = non-paralytic poliomyelitis.
⊕ = lesions were old; may be there as a result of previous inoculation.
○ = normal CNS histology.

K = sacrificed before end of 30-day period of observation.
* = tested in newly arrived, previously unused monkeys.
† = retested 7 months later; material held in lusteroid tubes at −70° C.
†† (and similar figures) = monkey serial number.

ing the availability of poliomyelitis virus in lymphatic tissues is not warranted. The erratic results were probably due in part to the recognized crudeness of the experimental methods.

Consideration must be given to several factors which could influence the results: namely, a) that poliomyelitis occurred in some of the monkeys because of the earlier inoculation with serum–virus mixtures or active poliomyelitis virus in titration studies, and b) the sacrifice of some of the monkeys early in the observation period because of scurvy, and prior to a time of expected experimental paralysis. Of 98 old monkeys used in these tests, only 2 on histologic examination had lesions which were not acute. Since these animals experienced a non-paralytic attack (Table 2), it was not easy to tell which inoculation had infected them. Although included in the data, they have not been considered postive tests.

The occurrence of experimental poliomyelitis within the expected incubation period (Table 2) and the presence histologically of acute lesions in the central nervous system following inoculation with extracts of central nervous system and lymph nodes in comparison with the majority of negative tests with pancreatic and mesenteric lymph node extracts indicate that the positive tests may be looked upon with reasonable confidence of being real isolations. In contrast, the monkeys which were sacrificed within 6 to 20 days after inoculation on the suspicion of having poliomyelitis, but which were actually ill with scorbutic pseudo-paralysis, cannot be looked upon as other than negative tests. One cannot be certain, however, that virus was not actually present in the latter lymph node extracts, especially in those monkeys sacrificed early in the incubation period.

Some monkeys may have become resistant because of previous inoculation. In view of the negative histologic results in 80% of the re-inoculated monkeys and the presence of subacute lesions in only 2 monkeys (2%), this appears to be an unlikely event. Another aspect of the problem is the possibility that specific antibody appeared early in lymph and lymphatic tissue[2,12] since it may be present in blood[10,14] of persons ill with poliomyelitis at, or a few days after, onset of illness. The observations that virus can be detected in lymph nodes from one side of the body and not the other indicate that the methods used were not delicate enough to provide more than a general notion concerning the actual presence of virus (or antibody) in lymphatic tissue.

Poliomyelitis Virus in Pancreatic Tissue. The pancreas was elected for study for 2 reasons. First, the source providing large quantities of poliomyelitis virus in the lumen of the intestinal tract of man has not been defined. Since the pancreas pours its exocrine secretions into the small intestine through connecting ducts it was considered a potential, although unlikely, source of poliomyelitis virus. Second, pancreatic tissue extracts, because of the enzymes they contain, might represent a more severe challenge to the reactivation of latent poliomyelitis virus than lymph node emulsion, thereby serving as rather crude controls. Pancreatic tissues obtained from 8 patients (1 sample was lost) were tested. Each of the samples was negative for poliomyelitis virus.

Distribution of Virus in Human Lymph Nodes. In an earlier paper[15] one of the authors included a tabular summary of reported data on studies made in an effort to detect poliomyelitis virus in lymph nodes other than tonsils in fatal human cases. In that study experimental data were added from a study of 3 patients, and the occurrence of virus in human axillary lymph nodes was pointed out. The present study re-

affirms some of the observations made earlier. To the tests recorded in the literature and listed in Table 3, 9 other cases are added which were studied in the laboratory and which form the basis of this report.

Discussion. Having in view the published data, to which the data of this report are now added, it would seem that the presence of poliomyelitis virus in certain regional lymph nodes was not accidental, and that the virus may have arrived there as a consequence of its being transported in extra-neural body milieu.

did not reach involved lymph nodes from mucosal surfaces, or from cutaneous areas soiled by excreta containing the virus. One fact which stood out prominently was the infrequent detection of poliomyelitis virus in mesenteric lymph nodes. In regard to this fact, these results agree with those reported previously. It might be expected that virus would appear in these nodes in view of the large mucosal surface exposed to it. The fact that virus was not found there very often at the time of death suggested that it penetrated the intestinal mucosa only occasionally, or

TABLE 3.—RESUME OF TESTS RECORDED IN THE LITERATURE FOR POLIOMYELITIS VIRUS IN LYMPH NODES OTHER THAN TONSILS IN FATAL HUMAN CASES

	Lymph Nodes				
Authority	*Cervical*	*Axillary*	*Inguinal*	*Mediastinal*	*Mesenteric*
Flexner and Lewis[5] (1910)	—	—	—	—	1/1*‡
Levaditi, Schmutz, and Willemin[11] (1931)	—	—	0/1	—	—
Flexner[6] (1936)	—	—	—	—	0/8
Kling, Olin, and Gard[9] (1938)	1/2	—	—	—	4/33
Kempf and Soule[7] (1940)	—	—	—	—	0/3
Sabin and Ward[13] (1941)	0/7	(1/7)†	(1/7)†	—	0/6
Kessel, Moore, Stimpert, and Fisk[8] (1941)	—	—	—	—	0/14
Wenner and Paul[15] (1947)	0/1	1/3	0/2	0/1	1/3
Fatal Human Cases, Univ. Kan. (1949–1950)	—	6/9	4/9	—	1/9
TOTAL	1/10	8/19	5/19	0/1	6/76

*1/1 = 1 test positive in a sample from 1 patient.
† = Axillary and inguinal nodes pooled.
‡ = More than 25 years later (1936) Flexner pointed out that sterile technique had not been used in this determination and so the positive result could not be accepted as definite. This test has not been included in the total.

Poliomyelitis virus may enter the lymph nodes from several broad anatomical areas and in several ways, namely, a) absorption from contaminated areas of the skin and mucous membranes, b) migration into ganglion cells and thence along nerve fibers supplying lymph nodes, and c) absorption from blood and extracellular fluids following the occurrence of a transient viremia during the invasive stage of poliomyelitis.

Few facts can be marshalled to reject the possibilities that poliomyelitis virus having crossed the intestinal membranes it had already disappeared, or was masked by a specific inhibitor. It is not an unlikely event that specific antibody had appeared first in these lymph nodes.

In a previous study, Sabin and Ward[13] found poliomyelitis virus in a pool of axillary and inguinal lymph nodes, as well as in a pooled mixture of lung, liver, spleen, and kidney from a patient who died 2½ days after onset of illness. In their comments on these findings, Sabin and Ward considered

the possibility that virus may be widely distributed in the early stages of the disease, but elected to consider, until further information was obtained, that virus in inguinal lymph nodes was there following transfer from perianal areas, and that possibly virus found in the lung had been aspirated from the alimentary tract. Objection can be raised now to one of these explanations in view of the presence of virus in axillary lymph nodes. On the basis of available knowledge of the anatomy and physiology of the lymphatic system no convincing evidence has been found of connections between afferent lymph channels of axillary nodes and the mucous membranes of the oropharynx, a site where virus can be found during the first few days of clinical poliomyelitis[6].

The contamination of cutaneous surfaces with poliomyelitis virus and its transfer to lymph, and thence to lymph nodes, does not appear to have been an event whereby virus gained a *primary* foothold in the bodies of the patients reported here. At the same time, one cannot exclude absolutely the occurrence of gross skin contamination following implantation of virus in the gastrointestinal tract. This idea has been rejected and without tangible proof. It has been quite difficult to believe that a diffuse and probably rather consistent soiling of most of the integument occurred in order to explain the widespread distribution of virus in regional lymph nodes.

The potentialities for movement of poliomyelitis virus in the peripheral nervous system are largely unknown. Howe and Bodian[5] have observed that transection of the spinal cord of monkeys failed to prevent virus inoculated below the transection from passing into the cord and brain stem above. It was their view that virus may have passed from the cord along sympathetic fibers to paravertebral neurones and after ascending in them reentered the cord. If such pathways were used, then it cannot be considered unlikely that poliomyelitis virus ultimately gained access to lymphatic tissue by centrifugal spread along postganglionic fibers supplying these structures. However, some evidence has indicated that fibers of fine caliber, such as are found in sympathetic nerves, were not especially susceptible to transmission of virus[5]. In view of these considerations, and particularly in the absence of crucial evidence, the likelihood of virus moving in neurones to lymph nodes must be viewed as a possibility until evidence to the contrary has been obtained.

A number of considerations, however, support the assumption that poliomyelitis virus may be brought to lymph nodes from extracellular compartments, and that it may appear there because of a widespread distribution of virus during the invasive stage of the disease. Wickman[16], Burrows[1], and others have called attention to a generalized hyperplasia of lymphatic tissues in rapidly fatal attacks of poliomyelitis. Burrows concluded from the histopathology of the human disease that the virus enters by way of the intestinal lymphatics and thence spreads to contiguous lymphatic tissues. Although human lymph nodes have shown hyperplasia, studies have not been made in regard to multiplication of virus within them.

The experimental evidence which is available does not readily support the opinion that a viremia occurs early in poliomyelitis. The train of events beginning with implantation and the final dissemination of virus previous to involvement of the central nervous system in human beings has eluded definition. Poliomyelitis virus has been recovered from the blood of patients twice[10,14] in recent years. The tests were made following onset of neuro-

logical symptoms and hence rather late in the natural history of the disease. In view of these meager data the probability must be considered that a viremia occurs early in the illness of these patients. Viremia, if it occurs, could appear as a result of the extension of virus from a nidus in the long gastrointestinal tract with outflow through lymphatic channels into the blood stream and interstitial tissue spaces. From these compartments virus could be transported to lymph nodes where it may be detected for a period after the stage of viremia.

At this stage of the study it is clearly necessary to recall the possibility that poliomyelitis virus in the human disease may be widely distributed in body tissues at a time preceding clinical evidence of involvement of the central nervous system.

Summary. 1. Following fatal illness caused by poliomyelitis virus, regional lymph nodes and pancreatic tissues were obtained at necropsy from 9 patients. Poliomyelitis virus was detected in lymph nodes obtained from 6 individuals. The positive tests were distributed as follows: right axillary lymph nodes, positive in 2; left axillary lymph nodes, positive in 3; right inguinal lymph nodes, positive in 2; and left inguinal lymph nodes, positive in 2 individuals. Poliomyelitis virus was found once in mesenteric lymph nodes. The pancreatic tissues obtained from these 9 individuals did not contain detectable amounts of poliomyelitis virus.

2. The published results on the presence of poliomyelitis virus in lymphatic tissue were reviewed, and the results of the present study are discussed in view of antecedent data.

3. The assumption is made, in view of a widespread distribution of poliomyelitis virus in lymphatic tissue, that during the invasive period, poliomyelitis virus extends from a position in the gastrointestinal tract into lymphatic channels with outflow into the blood stream and interstitial tissue spaces. From these compartments virus is transported to lymph nodes where it may be detected for a period after the stage of viremia.

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PATHOGENESIS OF MUSCLE NECROSIS DUE TO EXPERIMENTAL LOCAL COLD INJURY

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The pathogenesis of tissue necrosis due to local cold is not well understood. In general, there are two schools of thought: one, that tissue damage is secondary to vascular changes, that is, vasoconstriction, stasis with plugging of the capillaries with clumps of red blood cells, edema, or actual thrombosis[8,11,14,16-20,27]; and the other, that tissue necrosis is caused by direct action of cold on tissue cells[5,21,26,29].

Most pathologic investigations reported have concerned late changes following severe frostbite. Under such conditions early lesions cannot be studied, and also there is danger of regarding as primary, findings which in reality may be secondary to necrosis, infection, or both.

This study was made to clarify our knowledge of the sequence of events leading eventually to tissue death. Muscle was chosen as the tissue for investigation, since it is possible consistently to produce muscle necrosis by local cold without causing necrosis of overlying skin[25]. Such a closed lesion precludes the possibility of secondary infection from the surface, so common when the skin becomes gangrenous.

Materials and Methods. The experiments were performed on 83 male albino rabbits with a body weight of more than 2,500 gm. Sixty animals had one hind leg exposed to an alcohol bath of −12° C. for 30 minutes, a degree of exposure which has proved critical for muscle tissue[25]. The exact procedure is given in another paper[23].

After exposure the 60 animals were divided into 15 groups of 4 animals each. Those in the various groups were sacrificed at the following intervals after exposure: 15 minutes; 30 minutes; 1, 2, 4, 6, 8, 10, 12, 14, 16, 24, 48, and 72 hours; and 8 days.

The frozen legs were thawed at room temperature in air, except in those animals sacrificed 15 minutes after exposure. These were rewarmed in water at 42° C. for 5 minutes to insure complete thawing before death of the animal.

Immediately after death the anterior muscle group (tibialis anticus and extensor digitorum longus) of both the exposed and unexposed legs was removed and immediately fixed in 10% formalin. These muscles were investigated because muscle necrosis, which occurs in 95% of legs exposed to an alcohol bath of −12° C. for 30 minutes, appears first and is more extensive in these muscles. Necrosis appears first in the middle or distal portion of the belly of this muscle group.

After fixation, blocks were cut to include the distal two-thirds of the muscle group, embedded in paraffin, and sectioned. Stains used were hematoxylin and eosin and Mallory's phosphomolybdic acid for connective tissue.

In order to differentiate pathologic changes due to cold from artefacts caused by too early fixation, as described by Millar[22], the following was done. Twelve animals were exposed to the same standard cold injury and 2 of these sacrificed after 15 minutes, 6 after 30 minutes, and 4 after 2 hours. The anterior leg muscles of these animals were allowed to remain in the refrigerator overnight before fixation.

To be certain that the anatomical changes observed in the muscles of the frostbitten legs were not due to ischemia, 11 animals in 3 groups of 4, 4, and 3 were treated as follows. A tight rubber tourniquet was placed around the thigh of 1 hind leg just above the knee to occlude completely the blood supply to the limb. In 1 group of 4 the

tourniquet was allowed to remain for 45 minutes to correspond to the animals exposed to cold for 30 minutes and sacrificed after 15 minutes; in the 2nd group of 4 for 60 minutes to compare with the animals exposed to cold for 30 minutes and sacrificed after 30 minutes; and in the 3rd group of 3 for 90 minutes to correspond to the animals exposed to cold for 30 minutes and sacrificed after 60 minutes.

Results. GROSS FINDINGS. In all instances up to 72 hours after exposure the muscles which had been frozen displayed a diffuse, dull red color in contrast to the bright glistening red color of the muscles of the unexposed leg and of the legs rendered ischemic by tourniquets. A slight edema of the muscles in animals sacrificed after 15 minutes was manifested by an average increase in weight of 14% compared to the muscles of the unexposed leg. This weight increase gradually became greater through the 72-hour period, at which time it reached approximately 40%. Gross necrosis was visible after 72 hours.

MICROSCOPIC FINDINGS. Fifteen minutes after exposure many muscle fibers were swollen and many were extremely wavy. Numerous fibers presented a corkscrew appearance. Edema was manifested by the deposition of fibrin and eosinophilic granules in the spaces between muscle fibers and bundles. Many muscle cells showed degenerative changes consisting of irregularly shaped vacuoles, which in some areas were so numerous as to give the muscle fibers a fenestrated appearance. Some vacuoles were optically empty; others contained eosinophilic debris. Certain segments of muscle fibers were degenerated to such an extent that only a thin-walled honeycombed eosinophilic structure remained. Others showed complete absence of portions of muscle cells with or without absence of the sarcolemma. In the portions of muscle undergoing these changes, cross striations were largely absent; nuclei were absent in some areas of degeneration. The blood vessels were dilated and well filled with blood. No thrombi were observed; scattered areas of red cell extravasation were visible (Fig. 1). Sections taken from the same area of the unexposed leg (Fig. 2) and from the corresponding area of a leg that had been deprived of its blood supply for 45 minutes by means of a tight tourniquet showed no abnormalities except slight waviness of some muscle fibers (Fig. 3). The corresponding muscles of animals similarly exposed and sacrificed after 15 minutes, which were kept in the refrigerator overnight before fixation and subsequently sectioned, did not appear different from those fixed immediately.

Muscles from animals sacrificed 30 minutes after exposure showed the same changes as those sacrificed after 15 minutes but with more extensive degeneration of muscle fibers. Larger portions of some muscle cells had disappeared (Fig 4). The sections from the unexposed leg (Fig. 5) and from the leg of a rabbit rendered totally ischemic for 60 minutes by means of a tourniquet did not show abnormalities (Fig 6). Muscle kept in the refrigerator overnight before fixation did not appear different from that immediately placed in formalin.

One hour after exposure, vacuolation and fenestration of muscle cells were more extensive, and many segments of fibers, either singly or in groups, were completely degenerated. Replacing the segments of degenerated muscle were empty spaces (with or without an intact sarcolemma), eosinophilic granular debris, or shreds. There were small scattered areas of red blood cell extravasation. Interstitial edema, swelling of muscle fibers, and engorgement of blood vessels were pronounced. Thrombi were not observed (Fig. 7).

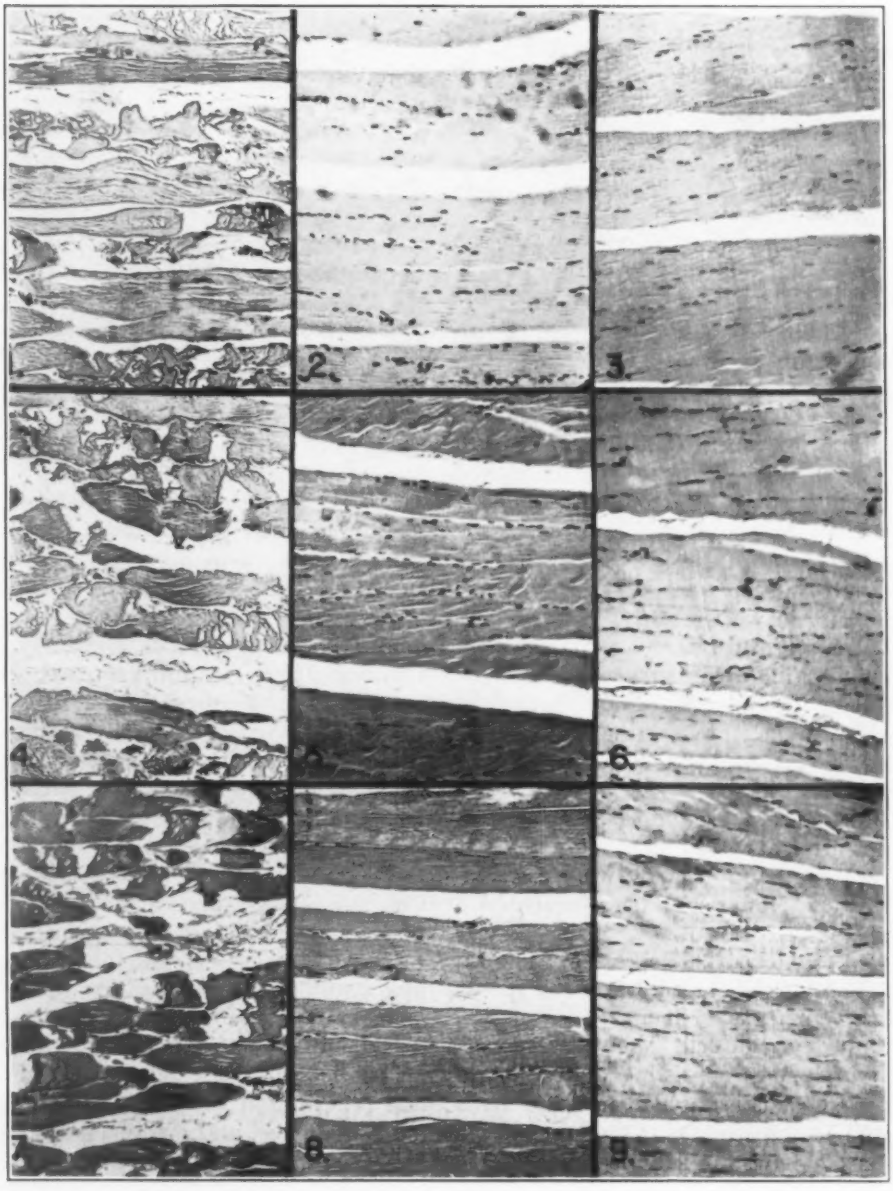

FIG. 1.—Section taken 15 minutes after exposure to −12° C. for 30 minutes, showing degenerative changes in the muscle cells. (X 128)

FIG. 2.—Control histologic section from unexposed leg of same animal as in Fig. 1. (X 128)

FIG. 3.—Section from muscle rendered completely ischemic for 45 minutes by means of tourniquet. Animal sacrificed immediately after ischemic period. (X 128)

FIG. 4.—Section taken 30 minutes after exposure to −12° C. for 30 minutes, showing degeneration of muscle cells. (X 128)

FIG. 5.—Control histologic section from unexposed leg of same animal as in Fig. 4. (X 128)

FIG. 6.—Section from muscle rendered completely ischemic for 60 minutes by means of tourniquet. Animal sacrificed immediately after ischemic period. (X 128)

FIG. 7.—Section taken 60 minutes after exposure to −12° C. for 30 minutes, showing severe degeneration of muscle cells. (X 128)

FIG. 8.—Control histologic section from unexposed leg of same animal as in Fig. 7. (X 128)

FIG. 9.—Section from muscle rendered completely ischemic for 90 minutes by means of tourniquet. Animal sacrificed immediately after ischemic period. (X 128)

Sections from the same muscle area of the unexposed leg (Fig. 8) and from animals whose same leg muscles were rendered totally ischemic for 90 minutes by means of tight tourniquets failed to show the abnormalities observed in the frostbitten legs (Fig. 9).

Sections from animals sacrificed 2, 4, and 6 hours after exposure showed progression of the degenerative process, which at the end of 4 to 6 hours was severe. At 4 and 6 hours large portions of many muscle cells were represented by aggregates of amorphous clumps of degenerated muscle. Others maintained their form but showed loss of cell architecture. Exudation of many polymorphonuclear cells was present in the animals sacrificed at 4 and 6 hours. The degenerating cells failed to stain well with eosin. Blood vessels were engorged but free of thrombi (Figs. 10 and 11).

Eight to 14 hours after exposure the muscle degeneration involved larger numbers of cells and extended over large areas. Cell exudation of polymorphonuclear and a few mononuclear cells was more pronounced. Small hemorrhages were fairly numerous. The vessels remained engorged, but no thrombi were observed (Fig. 12).

Sixteen to 24 hours after exposure, degenerative changes were more widespread. In some 16-hour animals the entire thickness of the anterior muscle group (tibialis anticus and extensor digitorum longus) showed necrosis. Cross striations were plainly visible in segments of many fibers which were the seat of severe degeneration in adjacent segments. In fact, in some fibers the cross striations were exaggerated and often the muscle cells were broken into narrow transverse discs at the striations. A definite increase in connective tissue, especially around blood vessels, was visible after 24 hours between muscle bundles, replacing degenerated segments of muscle cells (Figs. 13 and 14). The cell exudate, made up predominantly of polymorphonuclear cells, had undergone considerable degeneration. An occasional thrombus was observed in veins, and there were many small areas of hemorrhage.

After 48 hours numerous small and large mononuclear cells appeared in the exudate in addition to the polymorphs. There were many small masses of red cells between muscle fibers. Fibrosis was prominent near the margin of the necrotic zone and had replaced small areas of necrotic muscle (Fig. 15). In places numerous large mononuclear cells had phagocytosed necrotic muscle material (Fig. 16). In certain zones most of the muscle cells were in an advanced state of degeneration. Thrombosis of vessels was fairly often observed, and, in some cases, necrosis of the vessel walls was evident.

After 72 hours extensive proliferation of fibroblasts was observed near the margin of the necrotic area; this fibrosis had extended into the gangrenous zone, replacing much of the necrotic muscle, although islands of necrotic muscle were still visible (Fig. 17). In the central portion of the necrotic area there was no evidence of connective tissue proliferation, and all muscle cells showed extensive necrosis. Macrophages were numerous, and polymorphonuclear cells were less frequent. Vascular thrombosis was frequently observed, and necrosis of blood vessels was apparent. Signs of interstitial edema were either minimal or absent partly because of organization of the exudate.

While most of the muscle fibers of the grossly necrotic area showed complete loss of structure after 8 days, some retained their form. Others were represented by eosinophilic shreds and debris. There was no evidence of fibro-

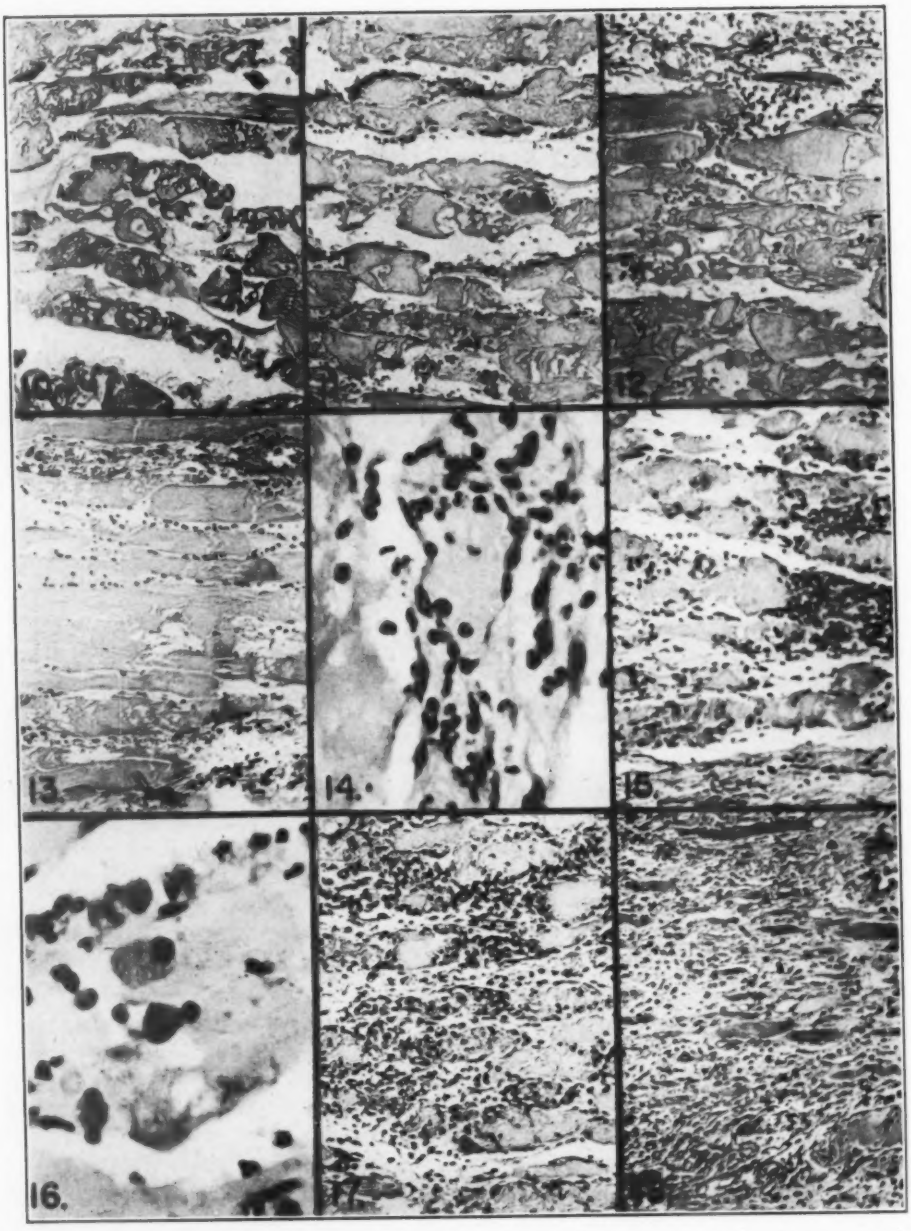

FIG. 10.—Section taken 2 hours after exposure to −12° C. for 30 minutes, showing progression of the degenerative muscle changes. (X 128)

FIG. 11.—Section taken 4 hours after exposure to −12° C. for 30 minutes, showing severe degeneration of muscle and exudation of inflammatory cells. (X 128)

FIG. 12.—Section taken 14 hours after exposure to −12° C. for 30 minutes, showing extensive muscle degeneration and increased exudation of inflammatory cells. (X 128)

FIG. 13.—Section taken 24 hours after exposure to −12° C. for 30 minutes, showing muscle degeneration, exudation, and early fibroblastic proliferation around blood vessels. (X 128)

FIG. 14.—High-power photograph of same section as Fig. 13, showing fibroblastic proliferation and inflammatory cells. (X 560)

FIG. 15.—Section taken 48 hours after exposure to −12° C. for 30 minutes, showing fibroblastic tissue replacing necrotic muscle cells. (X 128)

FIG. 16.—High-power photograph of same section as Fig. 15, showing macrophages containing phagocytosed debris. (X 560)

FIG. 17.—Section taken 72 hours after exposure to −12° C. for 30 minutes, showing marked fibroblastic proliferation replacing much of the necrotic muscle. (X 128)

FIG. 18.—Section taken 8 days after exposure to −12° C. for 30 minutes, showing almost complete replacement of the necrotic muscle with connective tissue. (X 128)

blastic proliferation; the cells of the exudate showed various stages of degeneration. Vascular thrombi were numerous. In areas near the margin of the necrotic zone fibroblastic proliferation was intense and largely replaced the dead muscle (Fig. 18). Remnants of muscle fibers were scattered throughout the areas of fibrosis.

Discussion. The sequence of events leading to necrosis of muscle tissue following exposure to local cold injury was one of continuous progression from the time of exposure. Both muscle and connective tissue became necrotic in the most severely injured areas. In the bordering zone only the muscle became necrotic, whereas the connective tissue remained viable and proliferated to replace the degenerated muscle.

In contrast to Friedman and others[11], who observed no muscle degeneration 2 days after experimental local cold injury in rabbits, degenerative changes were noted in the muscle fibers as early as 15 and 30 minutes after exposure, and marked changes after 4 to 6 hours. The muscles showed an increase in weight from edema and were discolored a dull, dark red up to 72 hours, at which time gross necrosis became evident. That these early changes were not due to ischemia was demonstrated by the normal appearance of muscles that had been rendered totally ischemic by means of tight tourniquets for periods of 45, 60, and 90 minutes; nor were they artefacts, since the muscles of the unexposed leg appeared normal. Blood vessels were dilated and engorged with blood, but thrombi were not observed before 24 hours, by which time muscle degeneration was well established.

It is not reasonable that the observed muscle damage progressing to necrosis was secondary to vascular changes. The more logical explanation is that the muscle changes were due to direct action of cold on the tissue cells, a true thermal injury. Whether ice formation within the cells, as suggested by Lewis and Love[21] and Blackwood[4], or some yet unknown alteration of metabolism was the cause remains to be determined. The fact that a number of investigators[8,10,11,14,17] have observed thrombosis of blood vessels in the late stages of frostbite necrosis is not *prima facie* evidence that it was the cause of the tissue necrosis. Other authors[13,21,26,27] have been impressed by the absence or rarity of thrombi observed in frostbitten tissue. Since the blood vessels of an extremity exposed to cold are also subjected to the same degree of injury as the other tissue cells of the leg, it should be expected that injury to vessel walls would occur, and under such circumstances thrombosis might develop. One is not justified, however, from such findings to conclude that the cold selectively injured the vessels and spared other tissues.

At least two investigators[16,20] are of the opinion that the tissue necrosis is secondary to plugging of the capillaries with red cell sludges described as occurring approximately 1 hour after thawing. Such a theory does not explain the acute degenerative muscle changes observed 15 and 30 minutes after exposure to cold and their absence in muscles rendered ischemic by tourniquets. Sludging of red cells is not peculiar to cold injuries. It has been observed in many diseases and conditions by Knisely and Bloch[15] and specifically in burns, the other type of thermal injury, by Brooks and coworkers[7]. It is an accepted view that necrosis from burns is due to the direct action of heat and is not secondary to vascular changes. Is it not conceivable that there is also a critical cold injury for each type of tissue beyond which recovery is not possible?

In addition to the 2 factors cited above (namely, failure to observe

thrombi in early necrosis and the occurrence of degenerative changes within 15 minutes after cold exposure), there is other evidence against the vascular theory of cold-induced necrosis. First, in some 2000 frostbitten rabbit legs, with either muscle necrosis or necrosis of skin plus muscle, necrosis of tendons has been seen rarely, and then only in late severe frostbite in which secondary infection was present. It is well known from clinical experience that tendons are very sensitive to interruption of their blood supply. Second, by means of a controlled standard cold injury muscle necrosis can be produced routinely without causing necrosis of overlying skin[25]. Certainly, under such conditions of exposure the vessels of the skin are subjected to injury as severe as that of the vessels in the muscle tissue. Third, the beneficial effects of rapid rewarming of frostbitten tissue reported by Arev[3], Fuhrman and Crismon[12], Finneran and Shumacker[9], as well as the authors[24], cannot reasonably be explained on the basis of preventing thrombosis of damaged blood vessels, since rewarming has not been shown to have an anticoagulant effect. Furthermore, rapid rewarming, which increases local tissue metabolism, would not be beneficial provided the theory is correct that ischemia due to thrombosis causes the tissue damage. Several investigators[1,2,6,28] have demonstrated either experimentally or clinically the increased rate of tissue death produced by the local application of heat to areas with diminished or absent blood flow and the beneficial results obtained by local refrigeration. As far as tissue necrosis was concerned, no reports have been found in the literature describing beneficial results from the local application of heat to ischemic tissue.

Even though the vascular changes during freezing and thawing are not considered by the author to be the primary cause of tissue damage, it is possible that they have some influence on the outcome of frostbitten tissue. However, it remains to be demonstrated whether vasodilatation with edema or ischemia from vasoconstriction or both are deleterious.

Summary. The pathologic changes in the muscle of cold-injured rabbit legs from the time of exposure to the time of well-developed necrosis are described. Microscopic signs of degeneration of the muscle cells were observed as early as 15 minutes after frostbite and were characterized by vacuolation, fenestration, and actual disintegration of segments of muscle fibers. At times, only a fine honeycombed eosinophilic structure represented the involved portions of the muscle cells. The pathologic process progressed gradually to complete necrosis, not only of the muscle but of connective tissue as well, and was grossly visible after 3 days. Acute exudation was demonstrable in 4 to 6 hours; fibroblastic proliferation began at the margins of the necrotic zone in 24 hours and was marked after 8 days. Vascular thrombosis was not seen earlier than 24 hours, was fairly often observed after 48 hours, and was more frequently found thereafter.

The findings described above were not observed in sections taken from the same area of the corresponding muscles of the unexposed leg; nor did sections of the same muscle area from legs that had been rendered completely ischemic for 45, 60, or 90 minutes show abnormalities.

Conclusions. 1. Degenerative changes in muscle are produced almost immediately after exposure to frostbite.

2. Such early changes cannot be due to ischemia from stasis, sludging of red blood cells, or thrombosis, since complete ischemia induced by the applica-

tion of a tight tourniquet for 45, 60, or 90 minutes failed to result in signs of muscle degeneration.

3. The primary cause of the muscle necrosis must be the direct action of cold on the tissue cells.

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RESPONSE OF PATIENTS WITH MALIGNANT AND BENIGN PEMPHIGUS TO ADRENOCORTICOTROPIC HORMONE AND CORTISONE*†

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From our present knowledge, pemphigus is a disease the structural anatomy of which lies entirely within the integumentary system. The particular site of disease is the epidermis. Its manifestation is the rapid appearance of localized collections of fluid, forming blisters, either within the epidermis or at its junction with the underlying dermis. Such blisters arise from an apparently normal skin. Subsequently signs of inflammation appear, due probably to secondary infection.

The cause of the disease is unknown. There is no evidence of an infectious etiology. Essentially, for some reason, the epidermal cells lose their cohesiveness and are torn apart by the migrating fluid from the dermis. The analogy is not too strained if one likens a blister to a wheal. The essential difference is the site of edema. The wheal resides in the vascular dermis; the blister in the avascular epidermis.

There are several varieties of pemphigus. All are characterized by the formation of blisters, either gross or microscopic. Whether all forms of the disease spring from the same source, we do not know. The diagnosis is wholly anatomical, conditioned by the ultimate history of progression in any particular individual. The malignant form is rapidly fatal, usually terminating in death from 6 months to a year after its onset. The benign form, of which there are several varieties, endures indefinitely. Of itself it is not fatal. It is only incapacitating. It may undergo spontaneous and permanent remission. Occasionally, however, chronic benign pemphigus may alter its course to a malignant and fatal termination.

Adrenocorticotropic hormone (ACTH) and cortisone affect substantially the course of all forms of pemphigus, however temporary that may be. Until the present there has been no therapeutic relief, not even temporary, it would seem. Treatment with these hormones, however, is not without its dangers. Nevertheless, all patients we have treated survived to walk from the hospital. Most have returned after varying periods of time in relapse. Over 6 to 12 months, 5 patients have been seen in from 3 to 4 relapses. On each occasion the response to treatment with ACTH or cortisone was

* The cortisone was supplied through the courtesy of Dr. J. M. Carlisle, Merck & Co., Inc., and the ACTH through Dr. John R. Mote of The Armour Laboratories, Armour and Company, and Mr. R. A. Lemon of Pacific Laboratories, Inc.

† Presented in substance May 1, 1951, before the Association of American Physicians, Atlantic City, New Jersey.

temporarily satisfactory. We here report our results in 17 patients with various types of pemphigus and treated with one or the other of these hormones.

Malignant Pemphigus. Four of our patients had severe malignant pemphigus. One was dangerously ill. All 4 were women ranging in age from 43 to 70 years. Their diseases had been present for 10 weeks to 14 months. Daily doses of 200 to 300 mg. of ACTH, in 4 equal divisions, given over a period of 22 to 45 days required to inhibit the disease and bring it into remission. The total dose in each patient was from 3 to 8 gm. Remissions following the initial treatment of the 4 patients lasted from 3 to 8 weeks. The longest remission, that of 6 months, was in a patient whose disease relapsed 3 weeks following the first course of ACTH, during which she received a total of 3.09 gm., and who received for the first relapse a total of 1.0 gm. of ACTH in 5 days with complete healing of lesions. At the third relapse, approximately 12 months following the first treatment, she responded satisfactorily, except for some residual erosions of the oral mucosa, to 20 and 30 mg. a day of ACTH given intravenously in 500 cc. of a 5% glucose solution over a period of 8 hours on each of 18 successive days. The total dose was 0.4 gm.

One patient had cortisone by mouth in daily doses of from 300 to 400 mg., reaching a total of 5.7 gm. in 23 days. With the exception of some mucosal erosions, a good remission was induced lasting 5 weeks. Lesions of the oral mucous membranes in malignant pemphigus are more resistant to treatment than are those of the skin.

In malignant pemphigus it appears that the use of either ACTH or cortisone is lifesaving. Complete healing of cutaneous lesions is attained and the lesions of the mouth either heal or are reduced in size and extent to a degree compatible with the comfortable taking of food. Left to its natural course, the malignant form of the disease progresses to denude larger and larger areas of the skin of its epidermis, resulting in the loss of plasma proteins and electrolytes and eventually in circulatory collapse. At the same time, involvement of the mouth gradually leads to impaired nutrition, for the taking of food and fluids becomes increasingly difficult.

Benign Pemphigus. There were 5 patients with benign bullous pemphigus who received treatment. Four were males and 1 a female, with ages ranging from 18 months to 76 years, but the ages of 4 were from 61 to 76 years. This is a disease chiefly of middle or later years, yet infants may be affected. The disease in these patients had been present from 2 to 18 months.

Unlike malignant pemphigus, where there is no attempt at regrowth of epidermis after the rupture of the bullae, the erosions of benign bullous pemphigus heal spontaneously. However, new lesions continue to form. The mucous membranes are not involved, or but rarely.

Approximately the same effective dose of ACTH was required to induce remission in these patients as in those with malignant pemphigus. In general, the response has not been so complete as in the malignant form. One patient was without a relapse for 12 weeks. Cortisone administered intramuscularly to one patient in daily doses of 300 and 400 mg. for 33 days effected a good remission for 5 weeks.

A second variety of benign pemphigus is marked by generalized exfoliation of the skin and slight to moderate exudation. Blisters are few and transient. Their superficial location in the epidermis beneath the outer horny

layer explains their failure to develop fully like those more deeply seated. This variety of the disease has responded less rapidly and completely than the other varieties. Yet when adequate doses of the hormones are given and continued for a long enough time there may be satisfactory resolution of lesions. The duration of remission seems to be less well sustained in exfoliative pemphigus. There was satisfactory resolution of lesions with both ACTH and cortisone in approximately the same dosage as was used in malignant and benign bullous pemphigus.

In a single patient, a youth of 18 years, whose disease had been present for 20 months, the intravenous infusion of ACTH in glucose solution, 20 mg. daily for 25 days, gave the best result obtained in all the patients treated. In this instance treatment was continued for a week or more after the resolution of all lesions when the skin had taken on a normal texture.

This boy had been treated 5 times previously, the remissions lasting scarcely long enough for him to leave the hospital. None had been longer than 4 weeks. Following total intravenous infusions of only 0.5 gm. of ACTH in glucose solution, all lesions had healed and except for a deep pigmentation, the skin looked normal. This was achieved in 25 days of treatment. The disease has now been in complete remission for 4 weeks.

Three of the 5 persons with exfoliative pemphigus were males and 2 were females. Their ages varied from 17 to 59 years. Their disease had been present for 8 months to 5 years.

In addition to the above patients there was one with the vegetative variety of benign pemphigus. In this there are exuberant granulomatous lesions in the intertriginous areas which develop at the sites of ruptured bullae. The lesions responded to treatment with ACTH. When the patient was last seen the disease had been in remission for 12 weeks.

The next, and final, variety of pemphigus affects the mucous membranes. Those of the eye, mouth, upper respiratory and digestive passages, and, in the female, the mucosa of the vagina and external genitalia may be involved. The disease leads to extensive scarring in the eyes and in the esophagus, larynx, and vagina to strictures. It may or may not be related to the other varieties of pemphigus. It resembles them only in the histological pattern of vesiculation. Blisters of the skin do not appear, although the disease may extend beyond the orifices of the lips and labia. Treatment with ACTH arrested the activity of the disease in 2 patients, both women, 69 and 72 years of age, respectively. There was no visible effect on the scar tissue. Relapse of activity occurred immediately.

The eosinophil response in all 17 patients was adequate whether at the initial administration of the hormones or at subsequent relapses. The reduction in the absolute number of eosinophils was always more than 50%. It was our impression, however, that healing of lesions was not accelerated until counts had been depresed in the range of 0 to 50 per c.mm. To bring this about it was often necessary to increase the daily dose of ACTH to the higher levels which we used.

There seemed to be no good correlation between the blood sedimentation rate and the activity of disease. In general the rate is increased by the disease. Sometimes it declined with the healing of lesions; at other times it did not. In some instances there was an increase in rate after treatment began and resolution of lesions was in progress. Thus, the sedimentation rate apparently provides no useful guide

by which to judge the activity of the disease.

Ill Effects of Treatment. The unwelcome results of treatment were not missing. The more frequent physiological effects of ACTH were observed, such as the moon face, hypertrichosis, hyperglycemia and glycosuria, and hypokalemia. Extensive and deep pigmentation of the skin appeared in 9 persons treated with ACTH. One patient, who developed the deepest pigmentation after intravenous administration of ACTH, had not shown any increase during treatment with cortisone. He was of Portuguese descent. No psychic aberrations were observed in any patient, except perhaps mild euphoria in some. There were 3 instances of large deep-seated gluteal abscesses developing at the site of the injection of ACTH which required wide surgical incision. Healing was slow, but eventually complete.

But there were more disturbing consequences of treatment. Two men aged 59 and 71 years, both hypertensive, developed congestive heart failure. In the first instance this followed the retention of sodium, but in the second it was thought a retention of water was caused by the high content of antidiuretic substance in the particular lot of ACTH. Failure followed immediately upon a rapid increase in weight in the presence of normal electrolytes in the blood serum. There was reactivation of a duodenal ulcer in one patient, and in another a similar lesion was suspected. This was not confirmed by roentgenologic examination.

One patient, a boy of 17 years, with exfoliative pemphigus developed an acute glomerular nephritis following one course of ACTH. Earlier in the disease he had extensive pyogenic infection of the skin as well as subcutaneous abscesses. Subsequently, treatment of a rapidly relapsing pemphigus with cortisone during the height of the nephritis seemed not to affect the severity of the nephritis. In later relapses ACTH was again given, both intravenously and into the muscles, without appreciable influence on the kidney lesion. Over a period of many weeks the signs of nephritis lessened in severity on a closely regulated dietary regimen.

The most perplexing episode occurred during the treatment of a patient with malignant pemphigus, who at the time it happened had received 8.2 gm. of ACTH intramuscularly over a period of 45 days. The lesions of pemphigus had partially healed. Without warning the woman lost consciousness and remained in a comatose or semicomatose state for 5 days, following which she gradually and completely recovered. Although treatment with ACTH was terminated, lesions of the skin and of the oral mucosa went on to complete healing.

There were no neurological signs in this patient to support a cerebral vascular lesion, which was suspected. She had shown none of the physiological effects of prolonged administration of ACTH either on physical examination or in the blood. The nearest conclusion was that there had been an acute metabolic catastrophe. The pemphigus in this person remains in complete remission after 9 weeks, and she has apparently suffered no ill effect from her experience.

In the absence of cardiorenal disease and electrolyte or protein imbalance, 5 patients receiving ACTH developed considerable pitting edema of the lower legs and ankles, and in addition one had purpuric lesions over the edematous areas. The edema subsided after stopping ACTH. One person showed urticaria and angioneurotic-edema upon cessation of treatment with ACTH, and another produced the typi-

cal livid erythematous lesions of erythema multiforme.

Comment. Alterations of tissue reactivity such as these in patients afflicted with pemphigus raise questions relative to the possible cause of this disease. The rebound of activity after stopping the hormones, with lesions of the skin characteristic of erythema multiforme or urticaria and angioneurotic edema, and the presence of edema of the dependent parts, like that frequently observed in association with the multiform erythemas, suggest the possibility of an allergic mechanism. Perhaps the response of the skin and the inhibition of blister formation itself are other indications of a similar nature. It may not be without significance in this connection that a chronic and severe urticaria over a year's period preceded the development of bullous lesions of malignant pemphigus in an elderly woman. Among the blisters were still to be found a few wheals, but it was not observed that the blisters were superimposed on any of them.

The diseases antecedent to pemphigus in the patients studied are not without interest. They may yield some information on the kind of person that pemphigus attacks, and afford some indication of the background of pemphigus. Three patients had a story of past urticarial episodes, another had asthma, and one, hay fever. One woman with malignant pemphigus was known to have had a duodenal ulcer 3 years before. There were 3 patients with hypertension, all asymptomatic. Hysterectomy preceded the onset of exfoliative pemphigus by 3 months in a woman 39 years of age, and one had an autonephrectomy, due probably to tuberculosis, but this was not proved. And, finally, chronic pyelonephritis was present in 2 persons.

It may not be going too far astray to consider a common factor in the genesis of pemphigus, the collagen diseases and rheumatoid arthritis or to find a common bond between the multiform exudative erythemas and pemphigus, if not an identity.

Summary. ACTH or cortisone were used in the treatment of 17 patients with pemphigus. Of these, 4 had the malignant form of the disease and 13 had benign pemphigus (5 cases of bullous pemphigus, 5 of exfoliative pemphigus, 1 of vegetative pemphigus, 2 of mucosal pemphigus). Satisfactory remissions were achieved by about the same dosage in all varieties, including malignant pemphigus, in which this therapy was lifesaving. There were noted some unfavorable side effects.

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FIBROUS DYSPLASIA OF THE BONES

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THIS protean disease is being reviewed under the title of "Fibrous Dysplasia of the Bones", as used by Lichtenstein and Jaffe[67]. An equally popular name under which many articles appear in the literature is "Albright's Syndrome". It must be pointed out, however, that reports of a great many cases have appeared under many other familiar titles, such as osteodystrophia fibrosa, juvenile Paget's disease, leontiasis ossea, osteogenesis imperfecta tarda, osteitis fibrosa, von Recklinghausen's disease of bones, fibrocystic disease, osteitis deformans juvenilis, and osteitis fibrosa cystica. These terms are often modified by reference to the distribution in the skeleton, as localizata, monostotic, polyostotic, focal, regional, unilateralis, generalizata, disseminata, and multiple foci, and also by reference to extra-skeletal manifestations of the disease such as brown patches in the skin, sexual and somatic precocity, hyperthyroidism, and other endocrine disturbances.

As can be gleaned from the long list of names, the main features of the disease, fibrous dysplasia of the bones, are varied and they are by no means confined to the skeleton. There are 3 seemingly disconnected chief features: 1) skeletal lesions affecting one, a few, many, or almost every bone in the body, 2) pigmented patches in the skin, 3) endocrine disturbances manifested by sexual and somatic precocity, especially in the female, and other endocrine disturbances. The skeletal lesions are an essential feature and may or may not be accompanied by either or both of the other two.

The disease fibrous dysplasia is one in a group of diseases in which softening, bending, and fractures of the bones occur. This group can be readily separated into two main divisions. In one the lesions are generalized in the bones with accentuations here and there; in the other, they are more or less disseminated in the skeleton, or even localized within a single bone, and exhibit a predilection for certain sites and patterns of distribution. The former comprises the deficiency and endocrine diseases, rickets, osteomalacia, osteoporosis, and hyperparathyroidism, and in this division specific causes and means of prevention and cure are known. The latter comprises Paget's disease, dyschondroplasia, osteogenesis imperfecta, and fibrous dysplasia, for none of which is there a known cause or a specific means of cure. All these entities now appear to be pretty well defined, but only after many years of intensive study by many investigators.

In order to give proper perspective to fibrous dysplasia within the group of malacic diseases of the bones, the following historical account is given of events leading up to the general recognition of the disease as an entity.

Historical Review. Just before the turn of the century several notable contributions to the pathology of the malacic diseases of the bones were made. Rickets had long been recognized as an entity and in 1885 the pathologic similarity of rickets and osteomalacia was pointed out, but many years passed before the common etiologic factor of these two diseases was discovered. In 1877 Sir James Paget thoroughly described the clinical and pathological features of the disease he called osteitis deformans but which now is better known under his own name. The two hereditary diseases, dyschondroplasia and osteogenesis imperfecta, have become well established entities. Von Recklinghausen[83] in 1891 published a lengthy report on 16 cases of bone diseases which he divided into 3 groups as indicated by the title, "Die fibrose oder deformirende Ostitis, die Osteomalacie und die osteoplastische Carcinose in ihren gegenseiten Beziehungen." The first group, deforming fibrous ostitis, comprised 6 cases, two of which, numbers 5 and 6, can be with certainty accepted as cases of fibrous dysplasia with widespread skeletal lesions. These 2 cases were designated as "verbreitete oder deformirende Ostitis mit Tumoren und Cysten", and "verbreitete oder deformirende Ostitis mit Tumoren", respectively. In his second group, with outspoken malacia of the bones, he included, along with 5 cases of osteomalacia and rickets, a case, number 7, with widespread skeletal malacia, which he called "Fibrose Ostitio, multiple Ostiosarkome". This case is generally accepted as one of hyperparathyroidism. Indeed, a parathyroid tumor was subsequently identified in von Recklinghausen's material from this case.

Following von Recklinghausen's article a voluminous literature, especially in the German language, rapidly accumulated, particularly concerning the less severe and more restricted skeletal forms of the disease. No attempt will be made to review the literature published prior to the discovery of hyperparathyroidism in the middle twenties. However, a few references to more pertinent articles published in that era are included.

Bloodgood[15], Barrie[10], Silver[91], and Meyerding[70] furnished valuable contributions to the American literature. Elmslie[36a] in 1914 published, in the *British Journal of Surgery*, under the title "Fibrocystic Disease of Bone", a lengthy and excellent discussion of the subject, well illustrated by many cases. He made distinctions between the sim

ple bone cyst, cysts which are formed by degeneration of giant cell tumors, and those cysts that are embedded in a complex of fibrous tissue in which are found bone of an atypical metaplastic type and cartilage (fibrous dysplasia). In the latter type of case he remarked on the bowing of the bones as well as the fractures and commented upon the prevalence of this type of lesion in the upper end of the femur and the frequency with which it was associated with involvement of other bones. He reported the case of a boy of 6 years in whom there were widespread progressive skeletal lesions and a nevus on the back of the neck. (This case was more fully reported by Bradfield[19] in 1931). Elmslie referred also to those cases with multiple sarcoma and secondary changes in the bones (hyperparathyroidism), and commented upon their bad prognosis.

Knaggs[59] in his book, "The Inflammatory and Toxic Diseases of Bone", 1926, described pretty thoroughly the skeletal features of fibrous dysplasia under the heading "Osteitis Fibrosa as a Primary Affection". In his chapter on leontiasis ossea he insisted that one of the two types which he described was the same disease as his primary osteitis fibrosa. Wieland[111] in 1922 published an article entitled "Osteitis Fibrosa Cystica Congenita". Apparently the disease under review was then a familiar pathological entity, at least in regard to the skeletal lesions.

The more severe forms of the disease with many bones involved had received less attention and in the then ignorance of hyperparathyroidism it was generally confused with that disease.

Morton[74], in the United States in 1922, reviewed the literature up to that year and reported an additional case under the title "The Generalized Type of Osteitis Fibrosa Cystica (von Recklinghausen's Disease)". The case he reported is typical of fibrous dysplasia. It concerned a robust man of 26 years who had sustained repeated fractures since the age of 3 years. Although many bones, including the skull, were involved, he was treated only on account of a painful and disabling coxa vara. There is an excellent gross and microscopic description of the bone exposed for osteotomy. Significantly Morton remarked about the thin, smooth cortex and the absence of the medullary cavity which was replaced with fibro-osseous tissue without cysts or giant cell tumors. In his review of 63 cases, he gave excellent accounts of 2 main groups, one of which can be easily recognized as fibrous dysplasia and the other as hyperparathyroidism, but in the further divisions of his classification and in his discussion he confused the 2 diseases. He remarked about the finding of parathyroid tumors at autopsies, in some of the cases, only to dismiss the matter as incidental.

In none of the above reports, except for Elmslie's reference to a nevus on the back of the neck in one of his cases, was any mention made of extraskeletal features of the disease. But in 1922 Weil[108] reported the case of a 9-year old girl who had pigmented patches in the skin and whose sexual and skeletal development was that of a girl of 15. She had menstruated since the age of 18 months and had sustained 8 pathological fractures. Radiographs revealed scattered skeletal lesions, referred to as an unusual variety of osteopsathyrosis. Calcium studies gave normal values.

In spite of the distinct difference between von Recklinghausen's single case Number 7, which can with certainty be accepted as one of hyperparathyroidism, and the cases, Numbers 5 and 6, in his first group, which are now recognized as fibrous dysplasia, the 2 conditions somehow or other subse-

quently became combined under the name of "osteitis fibrosa cystica or von Recklinghausen's disease of bones". This was unfortunate, as it no doubt hindered the appreciation of the significance of the finding of parathyroid tumors in some cases, but not in others. Yet these findings were made not without exciting suspicion as to the significance of the parathyroid tumors. In 1915 it was recommended that an attempt be made to remove a parathyroid tumor in a case of osteitis fibrosa cystica, but it was not until 1925 that this operation was performed with startling results.

About the same time parathormone was discovered and within a remarkably short time a vast amount of clinical and experimental evidence apparently proved that hyperparathyroidism caused osteitis fibrosa cystica*.

Von Recklinghausen's disease of bones and hyperparathyroidism then became synonymous. But it was soon noticed that in many cases of the osteitis fibrosa cystica of von Recklinghausen, neither hyperparathyroidism nor parathyroid tumors could be demonstrated even on surgical exploration. In 1929 Winter[113] reported a case of generalized osteitis fibrosa cystica in the absence of parathyroid tumor. Hunter and Turnbull[56], writing under the title "Hyperparathyroidism: generalized osteitis fibrosa", in 1931, included brief reports of 4 cases which they designated as "focal osteitis fibrosa". They were very emphatic about the distinction between the generalized osteitis fibrosa of hyperparathyroidism and the osteitis fibrosa in multiple foci. They were probably the the first to stress this distinction. Particularly they emphasized the vital importance of realizing that in the focal disease, even though many bones be affected, the condition is totally different from the generalized disease and that exploration of the neck for parathyroid tumors is unjustifiable. However, the cases that Hunter and Turnbull reported were of lesser skeletal extent and no mention was made of any extra-skeletal features, so that the overall account of the disease was not complete.

Jaffe[58a] in 1933, in a report entitled "Hyperparathyroidism (Recklinghausen's Disease of Bone)" found that he had a residue of cases of osteitis fibrosa cystica without parathyroid tumors. Concerning these, he expressed himself as follows: "My impression is that these cases are neither Recklinghausen's nor Paget's disease and that they constitute a still unidentified entity. I strongly suspect that they have a congenital basis."

It was becoming obvious that the "osteitis fibrosa cystica of von Recklinghausen" comprised 2 distinct and separate conditions. One was due to hyperparathyroidism; the other was not due to hyperparathyroidism.

Under the title "Osteitis Fibrosa", Dunninger[33] in 1931 published an excellent description of a North American Indian's skeleton estimated to be 1000 years old. The similarity of his illustrations to those of von Recklinghausen's cases, Numbers 5 and 6, is striking. In 1929 Ivimey[57] described a case under the title "Bone Dystrophy with Characteristics of Leontiasis Ossea, Osteitis Deformans and Osteitis Fibrosa Cystica". Pigmentation of the skin and predominantly one-sided skeletal lesions including the skull were

* A very charming account of the story of hyperparathyroidism can be found in Fuller Albright's Presidential Address delivered at the 29th annual meeting of the Association for the Study of Internal Secretions on June 6, 1947, in Atlantic City, New Jersey, and published in the J. Clin. Endocrinol., 8, 637-657, 1948.

present. The boy was blind and partially deaf.

Between 1929 and 1937 numerous cases like those described by Elmslie, Bradfield, Ivimey, Winter and Weil were reported by various authors[1,18,36b,38,41,42,46,47,49,53,55,81,93,94,99,112], under various titles, and Freund and Meffert[43] discussed the differential diagnosis and surgical treatment in 25 cases under the title "Localized Non-generalized Forms of Osteitis Fibrosa". Of special note is the case of McCune and Bruck[71a,b] of a girl with widespread disabling bone lesions, skin pigmentation, sexual precocity, and hyperthyroidism, which was most exhaustively reported in 1936 and again in 1937, and reference was made to the previously reported similar cases. This case was finally reported with autopsy findings by Sternberg and Joseph[97] in 1942.

In spite of Hunter and Turnbull's reference, in 1931, to the distinctiveness of the entity and how it differed from hyperparathyroidism, confusion between the 2 diseases still prevailed, as is attested by the fact that many of these cases were fruitlessly explored for parathyroid tumors. It remained for Albright and collaborators to bring order out of this confusion.

In 1937 Albright, Butler, Hampton, and Smith[4] reported 5 cases and a year later Albright, Scoville and Sulkowitch[6] added 2 more cases under the title "Syndrome Characterized by Osteitis Disseminata, Areas of Pigmentation and Endocrine Dysfunction with Precocious Puberty in Females". All 7 cases had severe skeletal involvement and skin pigmentation. With one exception all had sustained fractures. Precocious puberty had occurred in the 4 females and one of the boys was considered slightly precocious sexually. All 3 of the males had been previously explored surgically for parathyroid tumors without any having been found. The authors carried out most thorough investigations of their cases, including metabolic and endocrinologic studies. They reviewed the previously reported similar cases and pointed out how they differed from cases of other diseases affecting the bones, especially hyperparathyroidism. The focal nature of the lesions was again emphasized and is reflected by the use of "disseminata" in the title.

Lichtenstein[66] in 1938 published a paper based on 4 of his own cases, supplemented by 4 from other sources, under the title "Polyostotic Fibrous Dysplasia". There is a good clinical and pathological account of the disease affecting the skeleton in lesser degree. In none of his cases were extra-skeletal features of the disease present. The distinctive nature of the malady and its multiple focal distribution in the skeleton were again stressed.

The papers by Albright and collaborators and Lichtenstein stimulated interest in the disease and many more reports rapidly appeared in the literature, chiefly under the titles, Albright's Syndrome and Polyostotic Fibrous Dysplasia. By 1942 Lichtenstein and Jaffe[67] were able to collect 75 cases from the literature and to describe 15 more cases of their own under the title, "Fibrous Dysplasia of Bone". The change of title, from this source, infers that the skeletal lesions are not necessarily polyostotic. The authors give an excellent treatise on the skeletal pathology and an analysis of the 90 cases, as well as a thorough discussion of the disease in general. The many subsequently published reports and reviews add still more features to this already complicated and bizarre disease entity.

The following discussions are based upon the review of papers and books available to the Reviewer, and an analysis of 256 cases reported in articles

that were published mostly in the years 1929 to 1949.

Sex and Age Incidence, Onset, and Course. The sexes are about equally affected. Leaving out Schlumberger's 67 monostotic cases which were mostly in men from the armed forces, there were 83 males and 82 females among the cases in which the sex was stated. In 148 patients ranging from 4 months to 70 years of age, the disease could be traced to infancy in 7 cases, to childhood in 131, and to adolescence in 10. In 13 other patients between 20 and 57 years of age, the onset of symptoms or signs appeared before 20 years of age in two and after 20 in 9 while 2 were symptomless. In 5 of the older patients between 40 and 60 years of age, the duration of the symptoms was from 1 to 30 years. The oldest patient on record was described by Bingold[13]. The patient was a man of 70 who used a crutch and a cane and in whom the disease had started at 6 years of age. That the skeletal lesions can exist unnoticed, even in a widely disseminated form, is attested by the not infrequent accidental discovery of the disease on radiological examination for other reasons. A case in point is that of Sante *et al.*[86]. A young man, with a very large area of pigmentation on his trunk, had served for several years on active service as a combat pilot. When examined for an injury he was discovered to have widely disseminated skeletal lesions. The importance of the skeletal lesions to the armed forces and in the examination of inductees is brought out by Stauffer and Fitzgerald[96] and by Schlumberger[88].

The first sign of the disease may be precocious menstruation, but more often it is related to the skeleton, in the form of a limp, a pain, a bending of a bone, particularly the upper end of the femur, a deformity of the face or skull, or a pathological fracture. Occasionally failing vision sends the patient to the doctor[39,57]. With the exception of premature menstruation these patients are regularly reported as having a normal early infancy. Very often the first sign is a limp or a waddling gait appearing soon after the child begins to walk. Pigmentation of the skin was not reported as an attracting sign in any of the 256 cases reviewed.

The evolution of the skeletal lesions is very slow but usually reaches its maximum before maturity. There is, however, considerable variation in the progress of the skeletal lesions, and in the more severe forms deformities may become disabling fairly early in childhood. Recurring fractures are often the major disability. The progressive appearance of the foci in the skeleton is well authenticated, at least insofar as they are demonstrable by symptoms and radiography. Whether these foci are all established in the marrow at the same time has not been determined. Certainly individual foci extend and often coalesce. Acceleration of general growth in childhood and premature closure of epiphyses with cessation of activity of skeletal lesions concomitant with the closure of the epiphyses or at the normal maturation age is well attested. However, continuation of activity into adult life or activity manifest only in the adult often occurs. Reactivation after long periods of quiescence is not uncommon. In cases reported by Hunter and Turnbull[56], Dockerty *et al.*[31] and by Bonduelle and Claise[17] reactivation of childhood and adolescent bone disease occurred during pregnancy at 26, 34, and 33 years of age, respectively.

Skeletal Features. SKELETAL PATHOLOGY. The variations of the lesions in the bones are many, but they are all within the potentiality of the skeletoblastema to produce fibrous connective tissue, cartilage, bone, and synovial cav-

ities and to shift back and forth between the productive and lytic phases of the metamorphosis of the bones and joints. In brief, the process in fibrous dysplasia commences as a fibrous connective tissue proliferation within the medulla, replacing marrow and absorbing and replacing the cancellous and cortical bone. In this new-formed fibrous tissue metaplastic bone is laid down; occasionally islands of cartilage are developed and cysts may be formed.

Microscopic Appearances. There are many excellent descriptions of the pathological tissue removed surgically and occasionally at autopsy. The new-formed fibrous tissue varies from place to place in its composition. It may consist of small spindle and stellate cells and a finely fibrillary stroma in a loose or whorled arrangement, or it may appear in the form of intertwining bundles of larger spindle cells with plump vesicular nuclei and a varying amount of collagenous stroma. On the other hand, it may be poor in cells and highly collagenous, often retaining a whorled or intertwining pattern. Although the whorled arrangement of the connective tissue in fibrous dysplasia resembles that seen in neurofibromatosis, it cannot be accepted, by itself, as pathognomic of that disease as Thannhauser[100] contended. In the study of histological sections the Reviewer is impressed by the close relation of this whorled arrangement to the subsequent formation of bone trabeculae. Some areas may appear edematous and contain numerous small cystic spaces. The vascularity varies markedly. The vessels are thin-walled and usually small in caliber. The more cellular areas are more rich in blood supply. Here and there dilated vessels may be encountered with surrounding extravasations of blood, accumulations of multinucleated giant cells, deposits of hemosiderin, and occasionally some foam cells and a few lymphocytes. The two latter in no way represent part of the essential process and can be dismissed as incidental to hemorrhage and degeneration. The finding of foam cells cannot be interpreted as representing an essential xanthomatosis, an error into which some authors were led[92,93]. According to Lichtenstein and Jaffe[67], the giant cells are of small size with few nuclei, less than a dozen, and must be looked upon as multinucleated skeletal phagocytes. However, they are not the only type of giant cells encountered. Many authors describe cells indistinguishable from osteoclasts scattered or in conglomerations throughout the fibrous tissue. In 2 cases described by Dockerty *et al.*[31], giant cells with 50 to 60 nuclei were so numerous, in biopsy specimens, as to lead to the erroneous diagnosis of giant cell tumor. Osteoclasts may be found about islands of cartilage and around fragments of bone in well vascularized areas. Schlumberger[88] pointed out that these osteoclasts may persist after complete resorption of bone fragments and often appear in relation to small cysts. To the Reviewer the presence of osteoclasts, associated as they often are with evidence of bone absorption and increased cellularity and vascularity, is a manifestation of a shift to the lytic phase of bone building.

In the new-formed connective tissue, bone is characteristically laid down to a greater or lesser extent. It may appear as shaggy small masses or as irregular trabeculae. Isolated spheroids, bars or widely spaced, long curved, rather smooth trabeculae may constitute the bone content. On the other hand, ossification often appears in a more closely meshed anastomosing trabecular arrangement and may go on to form a dense uniform or irregular fine or coarse honeycomb structure.

The latter is beautifully shown in the incinerated specimens illustrated by Uehlinger[103] and Murray *et al.*[75]. Areas of fibrous tissue may escape ossification. It is the consensus of those authors who have made thorough pathological studies of material removed surgically or at autopsy that the nature of ossification is essentially metaplastic in the connective tissue, producing fiber type of bone. It is also pointed out repeatedly that osteoblasts may appear later along the margins of the metaplastic bone trabeculae. This has led some people to state that the process is one of osteoblastic bone formation, but lamellar bone formation is not a prominent feature. The osteoblasts observed suggest to the Reviewer that they play a part in smoothing off the irregular margins of the metaplastic bone trabeculae. Dockerty *et al.*[31] point out that fractures occurring in fibrous dysplasia heal by osteoblastic activity. Calcification occurs irregularly in the metaplastic bone, commencing centrally and leaving wide or narrow osteoid seams, depending upon the extent of calcification, or none at all if it is complete.

Osteoclastic resorption of the newformed metaplastic bone is commonly observed. One may then see, in the one specimen, productive metaplastic and osteoblastic bone formation along with lysis of bone by osteoclastic activity. The metamorphosis of bone in the pathological tissue is excellently illustrated by Schlumberger. The points of metaplastic bone formation are preceded by enlargement and proliferation of the connective tissue cells, then the deposition of osteoid between the cells and later calcification, and often points of osteoclastic absorption. In the quiescent phase, smooth, calcified osteoid trabeculae lie in more mature fibrous tissue, the one sharply demarcated from the other.

Islands of cartilage may be found in the dysplastic connective tissue. It is not usually a prominent feature but it was abundant in the cases reported by Telford[99], Revers[84], and by Bradfield[19]. Peripheral ossification and endochondral bone formation with the presence of marginal osteoclasts have been observed. In Schlumberger's 67 monostotic cases[88], cartilage was found only in relation to fractures. Albright *et al.*[4] relate the presence of cartilage in one of their specimens, to the epiphyseal cartilage. In the cases reviewed it was reported in 13, but most of the examinations were on only small biopsy specimens. That there is a relationship of the presence of cartilage to fractures is suggested by the fact that of the 13 cases in which it was found, 5 had had multiple fractures, 3 had 1 fracture, and in 1 the limb had collapsed and buckled. Furthermore, partial fractures are notoriously common in fibrous dysplasia and they are not always easily detected. However, in 2 of the 13 cases there was neither sign nor history of fracture and in others cartilage was found apart from fracture sites. Allowing for the development of cartilage in the callus of healing fractures, it is the belief of many authors that cartilage can be metaplastic in the fibrous connective tissue, as another manifestation of the potentialities of the skeletoblastema.

Cysts of various sizes may be encountered in the dysplastic connective tissue. They loom large in the radiological descriptions and in many of the reports from surgical sources, which include simple bone cysts and complicate matters still further by the reference to solid cysts. However, it is generally considered that cysts are not a very prominent feature of the lesions of fibrous dysplasia. When they are present, they are embedded in the dysplastic fibrous or fibro-osseous tissue

Microscopic cysts in edematous connective tissue may be numerous. Other small cysts may be found in association with bone absorption, increased vascularity, and hemorrhage. Larger cyst formation is about as common as the occurrence of cartilage. In the cases reviewed, cysts were reported 11 times, but again many examinations were made on limited amounts of tissue. They are variously described as ragged or with smooth, firm, fibrous walls and a content of watery or gelatinous consistency, clear or blood stained. Jaffe[58c] described the rapid appearance of a cyst the size of a standard football in a rib which was known to be the seat of a fibrous dysplasia.

Opinions vary as to the mode of cyst formation. Schlumberger[88] illustrated the formation of small cysts following the osteoclastic destruction of bone and its replacement by tissue fluid rather than by proliferation of connective tissue. Lichtenstein and Jaffe[67] attribute them to liquefaction of the connective tissue or possibly to hemorrhage or degeneration following interference with blood supply by marked fibrosis or radiation therapy. Sternberg and Joseph[97] believe that the cysts in their case were due to ischemia and hemorrhage, associated with resorption and subsequent liquefaction and necrosis. There can be little doubt that some of the cystic cavities are of degenerative nature. Yet there are cysts, described as having smooth, condensed fibrous walls and containing a clear watery fluid or a gelatinous coagulum; then there are the rapidly expanding types referred to above. These cysts are not easily explained by degeneration or hemorrhage.

To the Reviewer the cysts might well represent synovial cavities, albeit poor ones, produced by a process comparable to the formation of a joint cavity, a bursa, ganglia, cysts of the semilunar cartilage or Baker's cyst, all of which would come within the realm of the potentialities of the skeletoblastema. This hypothesis is supported by the case reported by White[109], in which there were widespread skeletal lesions of fibrous dysplasia and pigmented patches in the skin of a man of 57 years. The bone lesions had been progressive for 26 years and during the course of the malady numerous cysts, said to resemble ganglia, appeared in the fascial planes of the right thigh about the femur that was most markedly involved by the disease. An osteotomy, at the mid-shaft of this femur, for biopsy, revealed a cyst within the bone and embedded in dysplastic fibro-osseous tissue. All sorts of combinations and variations in the proportions of the above types of tissue are encountered, but the basic and predominant substance is fibrous connective tissue containing metaplastic bone in variable amounts.

The important matter of the absorption of preformed normal bone has not been described so often. Cancellous and cortical bone is absorbed by the proliferating connective tissue. The manner of absorption is referred to by Lichtenstein and Jaffe[67] as erosion, and by Falconer, Cope, and Robb-Smith[39] as attrition. The appearance is that of marginal reduction of the bone in the path of the advancing fibrous connective tissue, without the presence of osteoclasts, so that the line of demarcation between normal preformed bone and pathological connective tissue is quite sharp. The term attrition is hardly tenable as it indicates a process of wearing away by friction. Erosion is perhaps a more suitable term to indicate the replacement of bone without the usual appearance of lacunar or osteoclastic absorption.

In the experience of the Reviewer this type of absorption of the pre-

formed bone has been consistently observed. It is quite different from the cortical absorption in hyperparathyroidism which is osteoclastic and commences in the bone bed, affecting the marrow to a lesser extent and at a later time. Hunter and Turnbull[56], Garlock[45] and Falconer *et al.*[39] illustrate the comparative processes well. Many authors state that there is lacunar or osteoclastic absorption but it is difficult to determine whether they refer to the absorption of preformed normal bone or to the pathological metaplastic bone. Sante *et al.*[86] specifically state that the cortical absorption is osteoclastic and as an illustration they use a photomicrograph which undoubtedly demonstrates osteoclastic absorption, but this illustration is not identified as belonging to a particular case and therefore is not acceptable; besides, they are at variance with most other authors in demonstrating periosteal bone formation and in stating that the process originates within the cortex rather than the medulla and that it does not lead to deformities. It may be that their reference is to localized monostotic lesions of uncertain status, perhaps posttraumatic.

In the autopsy material from the case reported by Sternberg and Joseph[97], osteoclastic absorption of preformed bone was a prominent feature. However, their case was complicated by severe hyperthyroidism, which may have accounted for this histologic variant.

By progressive absorption the cortex becomes reduced to a thin layer. Ultimately it may completely disappear. The fibrous tissue then reaches the periosteum where it continues to proliferate, carrying the periosteum before it. However, there is no bony reaction on the part of the periosteum except in the event of fracture, and the surface of the bone remains smooth. During the process of cortical absorption, a common appearance is that of a thin strip of normal cortical bone sharply demarcated from the underlying pathological tissue which completely fills the underlying marrow cavity. Not infrequently the pathological connective tissue extends along the cortical canals for a short distance and, by erosion there, produces a cancellous appearance in the deep margin of the cortex. As this process advances toward the periosteum, the same cancellous appearance is seen in the remains of the subperiosteal cortical bone. Metaplastic bone formation may follow closely on the advancing fibrous tissue so that abnormal bone may become intermingled with the remains of preformed normal cortical bone.

Skeletal Distribution, Gross Appearance of the Bones and Deformities. As was stated at the outset, the skeletal lesions vary from the occurrence of a solitary lesion within a bone to a widely disseminated state with nearly every bone in the body involved. There may be several foci within a bone or the whole shaft of a long bone may be involved. Peculiarly the disease shows a tendency to a regional and one-sided distribution so that all or several of the bones of one limb may become diseased, or both limbs on the same side of the body may be attacked. More frequently the disease is bilateral in the limbs, and the axial bones, including the skull, are often affected. Even in widespread bilateral disease one side of the body is usually more affected than the other. The lower limbs are involved more often than the upper limbs. The bones of the hands and feet are not exempt.

In 134 of the cases reviewed, the lesions were monostotic in 28, in addition to Schlumberger's 67 cases. This number is by no means indicative of the incidence of monostotic lesions

in fibrous dysplasia, but because of the confusion with other localized lesions of bones, no attempt was made to sort them out. In only 11 cases was the location of the lesion strictly unilateral when more than monomelic. The more extensive bilateral and widely disseminated forms accounted for 86 of the cases. The lower limbs were involved 118 times and the upper limbs 87 times. The skull and face were involved 52 and 31 times, respectively, and the trunk bones 49 times. The most common site of involvement is the upper end of the femur.

A very important diagnostic feature of the disease is its focal nature in the skeleton. Uninvolved bones or parts of bones between the foci of disease retain their normal structure, which is in striking contrast to hyperparathyroidism in its effects upon the whole skeleton, by the process of absorption of bone. This was strongly emphasized by Hunter and Turnbull[56] in 1931 and reemphasized by Albright *et al.*[4] in 1937. It was the focal nature of the disease which led Albright to use the word "disseminata" rather than "generalizata" in the titles of his papers.

From the microscopic description the gross appearance of the bones can be anticipated. An affected bone may retain its normal bony structure and show only a focal replacement of the marrow by a solid fibrous mass containing more or less bone, or, still retaining its normal outward form, the cortex may be thin due to erosion by the expanding fibrous or fibro-osseous mass or the bone may become enlarged and irregularly expanded. A common description is that the periosteum is intact and normal or slightly thickened. The exposed bone may be pale, pink, or cyanotic. The cortex is thin or may have disappeared and the whole width of the bone is composed of a tough, soft or firm, white or brown fibrous-like tissue, more or less vascular and nearly always gritty as a result of new bone formation within it. Areas of marble-like bone may be encountered. The texture of this tissue varies widely *en masse* or in different areas. Usually it cuts easily with a knife; it may be softer than normal bone but still hard enough to require the use of a chisel or saw for cutting it; or it may be so hard as to turn the edge of an enterotome. In the case of marked curvature of the long bones, the concave side as a result of increased stresses usually is much harder and denser than the convex side. Not infrequently the soft gritty tissue is spotted by small hemorrhages. Islands of cartilage may be recognized and sometimes they are heavily calcified. Cysts of various sizes may be encountered and they are always embedded in fibrous or fibro-osseous tissue.

Replacement of the cortex causes a tendency of the long bones to bend, but because of the solid nature of the fibrous tissue, strengthened by the addition of new bone, the bending bone may still support the body weight even though the deformity be very great[27]. On the other hand, if the tempo of the process is slow and ossification keeps pace with the fibrous replacement of pre-formed bone, there occurs little or no bending deformity but only that of hyperostosis in the form of abnormal bone. At the same time progressive replacement of the cortex by tissue of lesser strength, sometimes aided by the formation of cysts, commonly leads to repeated fractures, often without much displacement because of the tough nature of the central dysplastic tissue in the bone; indeed, they may occur without loss of supporting function[45,106]. Fractures were recorded in 102 cases, some of which had sustained as many as 8. Almost invariably the fractures heal readily.

The most common deformity is the bowing outward of the upper end of the femur, often coupled with a marked coxa vara, producing appearances referred to as hockey-stick, shepherd's crook, jug-handle, and boomerang. The folding of the trochanter against the ilium often interferes with abduction of the limb and produces a scissor displacement of the thighs. The Reviewer has seen a figure-of-8 deformity resulting from this process with addition of a lateral U-bending of the legs. Deformities of the lower limbs may, as in the case of Murray *et al.*[75], almost defy description. The epiphyses are usually spared, but occasionally they may be involved, interfering with growth[4]. The Reviewer has seen shortening of a femur by 2 inches, the result of involvement of the epiphyses at both ends of the bone. On the other hand, overgrowth in the length of an involved bone was reported in 7 of the cases reviewed[43,45,50,57,84]. The Reviewer raises the question as to whether the elongation is due to the disease or is the result of fractures. It is well known that in the case of fractures of normal bones, elongation often occurs[14]. Six of the 7 cases had sustained fractures of the elongated bone, but Ivimey's case[57] had had no fractures and Revers' case[84] showed unusual elongation of the affected leg bones. Considering the expanding nature of the lesions and the often great extent of involvement of a bone, it is reasonable to the Reviewer that elongation as a result of the massive growth of pathological tissue should be expected, yet the factor of fractures cannot be ignored. There is no reason to believe that elongation of individual bones is due to epiphyseal overactivity.

The lesions in the skull usually assume a hyperostotic state. In only one of the cases reviewed was the skull cystic[72]. Commonly the base becomes greatly thickened and dense and bulges upward into the cranial cavity. The vault also thickens chiefly by replacement of the outer table. The process may be diffuse with the head enlarged symmetrically or it may be focal causing marked asymmetry. Large occipital and frontal bulges are common. Extension forward leads to facial deformities and obliterates the sinuses and the nasal passages, separates the eyes, and displaces them in a vertical or horizontal plane and may cause proptosis. Encroachment upon the foramina in the base of the skull may lead to optic atrophy and diminution in vision and hearing. Impaired vision was recorded 8 times in the cases reviewed. In Ivimey's case[57], the boy was totally blind and partially deaf. The 2 cases reported by Falconer *et al.*[39] were referred because of poor vision. Optic atrophy, choked disc and evidence of interference with the optic chiasma, and obliteration of one cavernous sinus were found. Compression of the spinal cord from an expanding lesion in a vertebra, twice requiring an operation, was reported by Jaffe[58c].

The bending of the long bones coupled with curvatures of the spine and deformities of the skull and face may give rise to grotesque deformities seen in no other condition.

Sarcoma is not a common complication of fibrous dysplasia of the bones, yet its occurrence is frequent enough to warrant suspicion of its presence when there is apparent reactivation of an old lesion in an adult. Elmslie[36a], in 1914, described a case of sarcoma and referred to 2 others. Knaggs[59] recorded the development of a sarcoma in the femur of a 53-year old man with monomelic fibrous dysplasia which commenced in early childhood. Alldredge[7] and Coley and Stewart[26] each reported 2 cases and Jaffe[58c] described another. Platt[80a] described 2 cases, and in a

survey of 170 cases of sarcoma of the bones found that 2 of the tumors originated in dystrophic cysts which had been present for several years[80b].

Skeletal Radiography. It can be presumed that lesions composed of fibrous, or noncalcified fibro-osseous, tissue and confined to the marrow cannot be detected radiographically, but with the appearance of calcification of the osteoid, the normal pattern of the overlying cortex becomes obscured and there is developed a localized medullary opacity varying according to the pattern and distribution of the new bone and its calcification. One may find then the dense homogeneous opacity of heavily calcified close-meshed honeycomb bone or the ground-glass appearance of close-meshed, trabeculated bone or translucent areas of fibrous tissue alternating with the opacities of calcified bone. As cortical absorption progresses the appearance will be that of the above covered by a thin cortex, and when the bone expands the cortex will be still thinner. With complete absorption of the cortex the diseased core will be covered only by the periosteum with no distinction between cortex and medulla. The appearance of the bones has been variously referred to as "ground glass", "smoky", "powdered chalk", "billowing", "smoke clouds", or a "filigree". The alternating areas of translucency and increased opacity has been stressed by Albright *et al.*[4] as distinctive of fibrous dysplasia and unlike the preponderant reduction of bone in hyperparathyroidism.

A long bone may expand to 2 or 3 times its normal diameter and is usually irregular. A flat bone may increase 6 to 8 fold or more in thickness. The thickened and irregularly hyperostotic vault of the skull, chiefly as a result of replacement of the outer table, simulates that of Paget's disease and accounts for the cases reported as juvenile Paget's disease. The occipital and frontal bulges and the grossly thickened, dense, hyperostotic base are all very characteristic. Involvement of the face bones in hypo- or hyperostosis with or without expansion, and the encroachment upon the sinuses and distortion of the teeth arrangements are also characteristic and give rise to leontiasis ossea. The lamina dura of the teeth, unless directly involved, is not altered as in hyperparathyroidism. An important feature is that uninvolved bone is normal. The bending deformities, the distribution of the lesions, and the precocious bone growth have been referred to previously. Worthy of special mention is the very common deformity of the upper end of the femur which bows outward as it is enlarged; coxa vara becomes more and more marked so that the limb may shorten as much as 5 inches. The bowed long bones usually show bony condensation along the concave margin. Recent or old fractures, partial or complete, and often with little or no displacement, are another common finding. There is no periosteal reaction except at sites of fractures. Appearances resembling Looser-zones have been described by Curr[27] and by Hernberg and Edgren[52].

Extra Skeletal Features. Pigmentation of the Skin. Patchy pigmentation of the skin, in small or large, single or multiple areas of brown, *café-au-lait*, or yellowish color, commonly accompanies the skeletal lesions. In the 256 cases reviewed, it was recorded 79 times. Its occurrence increases with the severity of the disease and it is nearly always present in those with precocious puberty or widely disseminated skeletal lesions but usually absent in limited bone involvement. In the 90 cases Lichtenstein and Jaffe[67] reviewed, it was recorded 32 times, but in Schlumberger's 67 monostotic cases[88] it was absent in all. With increasing aware-

ness of Albright's syndrome, the feature of pigmentation is less likely to be overlooked. Dockerty *et al.*[31] and Proffitt *et al.*[82] record its presence in cases of lesser skeletal involvement and Bennett[12] observed it in cases with monostotic lesions. The back, buttocks and thighs, shoulders, chest, neck, face, and scalp are the more common sites of pigmentation in that order of frequency. It may occasionally occur on the hands, lips, and buccal mucosa[79, 92, 100]. Albright *et al.*[4-6] emphasized the irregular margins of the patches as compared to the regular contour of the pigmented patches in the skin in von Recklinghausen's neurofibromatosis. The same authors also drew attention to the tendency for the pigmentation to be located chiefly on the same side of the body as that of the major bone involvement. When present, it had usually been noted when the patient was first seen. Commonly it is stated to have been present since birth, but not in a single case under review has the medical attendant been positive of this. On the other hand in cases under observation, it has been recorded as appearing at 2 years of age[41]. The earliest time at which the patches have been observed is that reported by Braid[20a,b], who noticed pigmented patches in 2 of his cases at 3 and 4 months of age, after recovery from icterus gravis neonatorum. Others have recorded their appearance between 4 and 24 months[71a,b, 90, 98]. The patches have been observed to spread[41]. There are a few reports on the pathology of the skin[5,31,63,95], and only hypermelanosis of the epidermis and a few underlying chromatophores have been found. No abnormality of the skin nerves has been observed. In none of the cases reviewed had pigmentation drawn attention to the disease. Its presence, in the absence of neurofibromatosis, suggests the existence of fibrous dysplasia of the bones.

Blood Chemistry. It has been generally believed that the calcium and phosphorous levels in the blood serum are normal and that a negative calcium balance does not occur in fibrous dysplasia. In the cases under review calcium estimations were reported as normal in 95 of the 124 cases in which the tests were done. In the remaining 29, levels between 11 and 13.8 mg. per 100 cc. were recorded. Higher figures were twice reported, 19.8[18] and 22.8[81]. Figures for phosphorous levels in 13 of the 97 cases on which estimations were done were between the 5 and 6 mg. per 100 cc. level, and in one the figure was 8[8]. Occasional figures as low as 1.8 were recorded. In view of the great preponderance of normal or high normal figures for calcium and phosphorus levels in the serum, tests should be repeated if unusual figures are obtained. That cases of fibrous dysplasia may be in negative calcium balance is attested by the fact that of the 29 cases on which calcium balances were carried out, 7 were losing calcium. Albright and Reifenstein[5] point out that excessive calcium in the urine does not differentiate between fibrous dysplasia and hyperparathyroidism. A persistent negative calcium balance in the presence of normal serum calcium and phosphorous values in a case reported by Garlock[45] led to a second exploration for a parathyroid tumor, even though all other features, including those of a bone biopsy, were characteristic of fibrous dysplasia.

The figures for alkaline phosphatase content of the serum were high in 37 of the 74 cases tested. In 12 they were between 20 and 64 Bodansky units or equivalents.

There were no consistent alterations in other chemical tests of the blood, but in 3 cases reported by Snapper[92]

and 2 by Summerfeldt and Brown[98] there was an elevation of the cholesterol levels in the blood serum above normal and in the 2 latter cases there was a decrease in carbohydrate tolerance.

Endocrine Features. In females, precocious menstruation is a common accompaniment of the skeletal lesions and is usually associated with pigmentation of the skin. Secondary sex characters appear concommitantly with or shortly after menstruation, and sometimes precede it. Among the cases reviewed 37 manifested precocious sexual development. In 34 premature menstruation had occurred. Its earliest appearance was at the age of 4 months[41]. In one case secondary sex characteristics were present in a 10-year old girl who had not menstruated; in another secondary changes appeared at 4½ years and disappeared at 5 years without menstruation[50]. Sexual maturity has been attained as early as 4½ years[71a,b]. Menstruation is usually not painful and is always irregular until normal pubertal age when it usually assumes the normal cycle. In one case of precocious menstruation, the menses ceased at the age of 15 and did not recur until the girl was 18 years old[90]. Sexual precocity is not incompatible with normal maturity, as 4 of the cases reviewed bore normal children after marriage[4,17,32,56]. Albright and Reifenstein[5] point out that the premature menstruation is not accompanied by cramps because there is no secretory activity of the endometrium. In 2 cases that came to autopsy, no evidence of ovulation was found in the ovaries[6,97]. Albright *et al.*[3,4,5,6] discuss the endocrinological features at length. They point out that follicle stimulating hormone is produced prematurely but not in excess and that luteinizing hormone is not produced prematurely. However, cases of precocious sexual development in the male have been reported in the literature. Sometimes the reverse of precocity occurs in both sexes and sexual development is retarded[39,52]. In one of the cases reported by Dockerty *et al.*[31], on labium was enlarged at 3 years. There were multiple bone lesions and pigmentation of the skin. Menstruation did not appear until the patient was 12 years of age. Kurzrok[62] reported sexual precocity commencing between 6 months and 18 months of age in 3 girls who had neither skin pigmentation nor demonstrable bone lesions. The precocity was looked upon as functional as there was no endocrine or central nervous system disease to account for the precocity. Whether these cases represent an incomplete form of Albright's syndrome is problematic. Bone lesions might have appeared at a later age.

In the male sexual precocity is very much less common and was recorded in only 5 of the cases reviewed[4,28,39,106]. As in the female, occasional retardation of puberty and hypogenitalism may occur[40]. In the case reported by Moehlig and Schreiber[72], the adolescent boy manifested gynecomastia and other feminine features and in Revers' case[84] a degree of dystrophia adiposogenitalis was present. In both of the cases of Falconer, Cope and Robb-Smith[39] features of acromegaly were reported; the jaw was prognathous, the hands and feet were unduly large, and the tongue was overgrown. In a boy of 13 the left breast was enlarged and the left testis was twice normal size[101]. Acceleration of growth and advance in skeletal age are often manifest in childhood. Another common sign of somatic precocity is premature fusion of the epiphyses, so that many of the adults are small of stature in spite of the rapid growth in childhood. In the cases reviewed 20 were reported as showing evidence of precocious skele-

tal development radiologically and several others are referred to as undersized adults. This feature is probably more common than is reported. Falconer, Cope, and Robb-Smith[39] suggest that skeletal prematurity is a more constant sign of precocity than are sexual changes.

Nervous System Signs and Symptoms. The mechanical effects of pressure on the spinal cord and cranial nerves already have been referred to. Most of the patients enjoy good health and most were reported to be normal mentally. Five patients were described as mentally retarded while 3 others were referred to as of unusually high intelligence. Some of the children were reported as shy and not very bright and subject to tantrums. Considering their handicap and interference with schooling, frustration complexes are not unexpected, as pointed out by Falconer *et al.*[39]. Albright *et al.*[4] found diminished abdominal and cremasteric reflexes in one of their cases. The pigmentation of the skin is perhaps a manifestation of an endocrine disturbance. Hyperthyroidism was prominent in 3 cases[5,9,71a,b] and of minor degree in 6 cases[23,46,60,98,100].

Hypertrophy of the nasal mucosa was a troublesome feature in a female case reported by Albright and Reifenstein[6] and was considered to be an effect of estrin. Troublesome nose bleed was recorded in reports of 4 male cases[77,81,104].

Other Extra-skeletal Features. A congenital arteriovenous aneurysm of the left arm was an additional feature in a case of a 19-year old male with multiple bone lesions and skin pigmentation[95]. A boy of 13 who died of acute pancreatitis and came to autopsy had a coarctation of the aorta and a small aneurysm of the ascending aorta. The right kidney and adrenal gland were smaller than normal and the testes were undersized[25].

Whether these anomalies are part of a more widespread congenital anomaly or merely fortuitous is difficult to determine.

In Euhlinger's case[103] there was a fibroma in the muscles of the calf which was described as identical with the fibrous tissue within the diseased bones.

Etiology. In spite of all the interest and effort applied to the etiology of fibrous dysplasia, no satisfactory explanation of the cause of the disease has yet been offered.

That fibrous dysplasia has often been mistaken for hyperparathyroidism is attested by the fact that 31 of the cases reviewed had been fruitlessly subjected to surgical exploration for parathyroid tumors. In several cases the operation was repeated. Fibrous dysplasia is not due to hyperparathyroidism.

There is no evidence that the disease fibrous dysplasia is hereditary or familial, nor is there any positive proof that any of the manifestations of the disease are congenital, even though most of the theorists believe that it is due to some sort of congenital defect.

Braid[20b] in 1939 built up a theory of liver disorder as a cause of the disease, because the 2 patients whom he reported suffered from icterus gravis neonatorum. But since the true cause of icterus gravis neonatorum has been discovered, his theory can be discarded.

Lichtenstein[66] and Lichtenstein and Jaffe[67] contended that the disease as a whole represents a congenital anomaly and that the skeletal lesions, in particular, are due to a perverted activity of the specific bone forming mesenchyme.

Moehlig and Schreiber[72] invoked a hereditary dyspituitarism as a cause and explained the unilateral distribution of the skeletal lesions on a basis of unbalanced chromosomal aberration.

Albright and collaborators[4-6] regarded the localization of the skeletal lesions as precluding an endocrine or metabolic basis for the primary cause of the disease and suggested, after thorough study of their cases, that the whole syndrome may be the expression of an embryological defect or of a disseminated neurological disturbance, the gonadal and other endocrine anomalies resulting from afferent nerve impulses from the hypothalamus to the anterior pituitary gland. The endocrinology they discussed at length, and in support of their theory quoted MacMahon, who found at autopsy in his case a discrepancy in the size of the mammillary bodies and a disturbance in the distribution of nuclei in the hypothalamus. In the cases of Sternberg and Joseph[97] and Coleman[25], however, no abnormal conditions were found in the brain.

Thannhauser[100] suggested that the endocrine disturbances were the result of pressure on the base of the brain by the thickened base of the skull. Among the cases reviewed, most of those with sexual precocity showed involvement of the skull, but Albright[4], Snapper and Parisel[93], Robson and Todd[85] and Braid[20a,b] stated specifically that in some of their cases with sexual precocity the skull was not involved. In several the skull was not mentioned, and in many with skull involvement no endocrine disturbances were reported.

Sternberg and Joseph[97] rejected the idea that a developmental defect can explain the sequence of events observed in fibrous dysplasia. They expressed belief that the syndrome is the result of a complex endocrine disturbance and that the bone lesions can be explained on the basis of a disturbance of metabolism. They invoked the idea of a local tissue susceptibility to explain the focal and regional distribution of the bone lesions.

Thannhauser[100] attempted to show that fibrous dysplasia is but a manifestation of von Recklinghausen's neurofibromatosis while Snapper and Parisel[93] and Snapper[92] believed that their cases were due to xanthomatosis without Hand-Schüller-Christian syndrome. However, both these ideas were pretty thoroughly discredited by Jaffe[58b] and Albright[3] in defending the position of fibrous dysplasia of bone as an entity.

Helfet[51] put forward the hypothesis that fibrous dysplasia is the result of chronic hyperparathyroidism caused by hyperphosphatemia. On this basis he proposed the administration of aluminum acetate or gluconate to precipitate part of the phosphate in the bowel in order to prevent its absorption. Helfet recorded favorable results of this treatment in a small group of cases.

Murray, Kirkpatrick, and Forrai[75] lent little support to the view that the skeletal changes result from primary perversion of the bone forming mesenchyme. They believed that the bone lesions are due to some extra-skeletal disorder of calcium–phosphorus metabolism, a part of a congenital anomaly with an incidental localizing mechanism.

Schlumberger[88] in his report on 67 cases of monostotic fibrous dysplasia concluded that monostotic fibrous dysplasia is not a congenital anomaly, and etiologically probably has nothing in common with the form of fibrous dysplasia found in Albright's syndrome. He felt that it probably represents a disturbance of the normal reparative processes following any of a variety of bone injuries. The exact mechanism of cause and effect he admitted is not clear. He further presented evidence which suggests that the so-called ossifying fibroma and nonosteogenic fibroma of bones are but variants of localized fibrous dysplasia.

Conclusion. Fibrous dysplasia of the bones appears to be a distinct disease entity, the cause of which is not yet known. The peculiar skeletal lesions leading to fractures and severe expansile and bending deformities, the frequently associated pigmentation of the skin and endocrine disturbances; the appearance of the disease in early life and its preponderant activity during the growth period have been responsible for a number of different etiologic theories, most of which favor some sort of congenital anomaly.

The localization of monostotic lesions of the nature of fibrous dysplasia presents another problem. The Reviewer is of the opinion that the skeletal lesions of fibrous dysplasia as they appear in the polyostotic form of the disease and in Albright's syndrome can exist as a localized lesion in a bone, and he cannot agree with Schlumberger that localized monostotic fibrous dysplasia is always a response to injury. Considering the limitations of the types of tissue that can evolve from the skeletal tissue from whatever stimulus, the Reviewer believes that it would be a mistake to include under one etiologic factor all the localized monostotic lesions that resemble one another, because of the danger of disguising several different entities under a name for one of them.

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PREVENTIVE MEDICINE AND EPIDEMIOLOGY

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WHOOPING COUGH AND ITS EPIDEMIOLOGICAL ANOMALIES

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AND

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WHOOPING cough holds a traditional place among "the common communicable diseases of childhood." The generic use of that term implies that the diseases in the group have a number of common epidemiological attributes. For one thing, all of the illnesses are anticipated as a usual experience of persons living in an ordinary environment; and secondly, infection occurs relatively early in life. Since the term, common communicable diseases of childhood, specifies disease, the infectious process should be clinically definite and commonly classical in its manifestations. Other infectious agents may be as ubiquitous, but not so regularly productive of recognizable disease, expending a goodly part of their force in inapparent or subclinical infection. Because of the prescribed limitation to childhood, these diseases are clearly immunizing, leading to more or less permanent resistance and a general absence of second attack. Finally, the diseases are benign, for with attack so nearly universal, man would otherwise scarcely have survived.

Currently, and in the United States, measles, mumps, rubella, chicken pox and whooping cough are the 5 diseases included in the group. However, the history of epidemic disease is sufficient proof that at other times and in other places the list has differed. Two centuries ago, when "most born in London have smallpox before they are 7,"[26] variola was if anything a commoner disease of childhood in Britain than measles. Typhoid fever in Greece is today[160b] so frequent among children as to suggest its inclusion among childhood diseases of that country; and malaria would be a choice in many lands.

Diphtheria, poliomyelitis, and meningitis are equally common infections of childhood but are by no means common *diseases* in the sense of measles and mumps. Inapparent and atypical infections are a strong feature of all three;

and the frequency among adults also gives evidence of a more limited distribution in childhood. Scarlet fever occurs more frequently in the United States than any of the three just mentioned, but again has a goodly component of inapparent infection, and many persons escape entirely. Furthermore, an attack of scarlet fever immunizes only against an erythrogenic toxin and not against streptococcal infection. Smallpox has disappeared from consideration as a disease of childhood.

Roseola infantum, infectious mononucleosis and infectious hepatitis are too ill-defined epidemiologically to be placed securely. Roseola infantum might well be included in the group, were better clinical recognition possible and reporting practiced, for the disease is limited to infancy and childhood. The appreciable incidence of infectious hepatitis and infectious mononucleosis among young adults suggests that both are more like diphtheria of today than measles, being neither so common nor so clearly characteristic of childhood.

As causes of death in childhood, the diarrheas and dysenteries along with the pneumonias rank higher than any other infection. They are frequent diseases but not so nearly universal; and they are neither immunizing nor characteristic of childhood.

Whooping cough, like other mass diseases of human populations, conforms in its origin and behavior to the basic biologic laws of ecology[58]. Its inclusion among common communicable diseases of childhood is indication of epidemiological features more or less common to the five diseases named. Nevertheless, within that group and among mass infections generally, whooping cough occupies a position that in many respects is anomalous[57], sometimes individual and distinctive, and occasionally surprising in the form it takes. The severity of whooping cough, for instance, is much underrated, both in the direct and the indirect damage it causes to the health, growth and resistance of young children[41b]. Age distributions are atypical and sex differences unique. Deaths are inordinately frequent among infants aged less than one year. As a world problem of preschool children, whooping cough is in the front rank of acute infections, whether classed as common or uncommon diseases. School children lose more days from whooping cough per case than from any other infection. Despite all this, the disease continues to be lightly regarded by the public and also by many physicians[159].

Epidemiologists have never accorded pertussis the attention it warrants. The pathogenesis of the disease, the available knowledge of the infectious agent, and the nature of immunity reactions suggest that the epidemiological behavior of whooping cough should be easy to predict; but whooping cough does not always behave according to expectation. Curious paradoxes are encountered, both in relation to other diseases, and as pertussis behaves in various regions. The curious epidemiology of whooping cough is matched by its curious history.

History of Whooping Cough. The Hippocratic writings[68] contain descriptions of mumps so detailed as to establish epidemic parotitis as scarcely changed from that day to this. Others of the common diseases of childhood can be readily identified in older writings, notably the account of measles by Rhazes[16]; but not so whooping cough. The first adequate description is by Ballonius[3], who presented the disease as it existed in Paris in 1578. He took pains to note that he knew of no previous writings, but he spoke of his Tussis Quinta as a well established disease. Creighton[26] later searched available sources with equal lack of success, and

no one has been able to date whooping cough more remotely than a few decades before 1578. Creighton concludes with good reason, however, that whooping cough was not then a new disease, but merely new to doctors; and that in all probability it had existed for a long time. Sydenham[147] in 1679 introduced the name pertussis. Not until the eighteenth century is a succession of accounts of whooping cough met with. It is unusual that such a distinctly marked disease should have had no earlier record. If as common as it is now, its place in infant mortality should have been great.

Whooping cough was introduced into the American colonies at an early date, just when is not known. At least "in 1649 the people of Plymouth fasted on November 15, because there was an epidemic among the children of chincough and the pockes;"[114] and Noah Webster[154] states that "Hooping cough prevailed in many parts of the country in 1791". An early American description of the disease, entitled *An Essay Concerning Tussis Convulsiva or Whooping Cough*, was by Benjamin Waterhouse[153] (1822).

Radbill[119] gives interesting information on the origin of the various names by which whooping cough has been known, and tells of superstitions and treatments in vogue during past years. The monographs of Sticker[142] (1911), of Pospischill in Vienna[118] (1921) and the recent work of Lapin[82] are other sources for the history of whooping cough.

WHOOPING COUGH AND OTHER ACUTE COMMUNICABLE DISEASES OF CHILDHOOD. The data on cases and deaths to be had from official reports of health departments serve as one means to judge the relative position of whooping cough among other acute communicable diseases of childhood; and additionally to determine the absolute weight of the disease as a factor in the health of children. Deaths from whooping cough were first reported in Britain through the London Bills of Mortality, in 1701. They have been reported in the United States for variable periods, depending on the year when political units were admitted to the Registration Area established in 1880. In a few instances, morbidity records are available for certain states and cities since 1910; and for the entire country, with the exception of two states, since 1925. Prior to these dates the disease was not reportable in most states. The demographic data have inherent and serious limitations.

Deaths are reported with relative completeness, but not necessarily with exactness. A comprehensive survey showed that 36.7% of deaths from whooping cough were reported not as whooping cough but as due to other causes, principally pneumonia.

Case reporting is notably incomplete and for whooping cough varies from 3% to 64% in some few communities[41a]. In most localities and over the years, the level of reporting has improved, a factor to be considered in judging apparent increases. Relative frequencies are difficult to determine from reported cases, because some diseases are well notified and others poorly. Numbers of reported cases are consequently without much value in judging morbidity over an extended period, and for short periods the data may reflect the wider fluctuations but do not necessarily measure them[67]. Other epidemiological information is often of more value in determining the extent to which a population is affected by a disease, and in assessing the manner in which it moves through a community. With understanding of these limitations, existing data of the United States during recent years are examined with the purpose

of relating whooping cough to other acute infections of childhood.

Mortality of Selected Diseases. Age specific death rates for acute communicable diseases of childhood in the United States are presented for the available years of the past decade, (Table 1). Under age 1 year, whooping cough caused almost 3 times more deaths than the sum of all diseases listed in the table. At ages 1 to 4 years, rates for diphtheria and whooping cough were equal, but much in excess of the others. The rates for measles, so commonly coupled with those of whooping cough in epidemiological enteries cause more deaths of children than does whooping cough; but for those diseases the differences are great and they hold for all ages.

The inference to be drawn from these data is of the dominant position of pertussis among common communicable diseases as a cause of death among pre-school children, and to a lesser extent for all children aged less than 15 years. Much the same situation holds for the principal European countries. In recent years (1946 to 1949) whooping cough is consistently first among acute communicable diseases at age less than 1 year; and also at ages

TABLE 1.—ACUTE COMMUNICABLE DISEASES OF CHILDHOOD. MEAN ANNUAL AGE SPECIFIC MORTALITY RATES PER 100,000 POPULATION, UNITED STATES REGISTRATION AREA, 1940 TO 1948.

	Age in Years				
Disease	*0–1*	*1–4*	*5–14*	*0–14*	*All Ages*
Whooping cough	64.0	6.4	0.2	6.6	1.6
Measles	10.9	4.5	1.0	2.9	0.9
Mumps	—	—	—	—	0.0
Chicken pox	—	—	—	—	0.1
Rubella	—	—	—	—	0.0
Scarlet fever	0.7	1.0	0.6	0.7	0.2
Diphtheria	3.5	6.5	1.3	3.0	0.9
Poliomyelitis	1.8	1.7	1.9	1.8	0.8
Meningitis	9.2	2.8	0.8	2.0	1.0

Source: Vital statistics of United States, U. S. Department of Commerce and Federal Security Agency.

interpretation, are scarcely of comparable order. For diseases of this class, whooping cough during the whole of childhood, 0 to 14 years, occupies first place as a cause of death, with diphtheria second and measles third.

Pertussis is also a more important cause of death than tuberculosis for infants aged less than one year, with rates of 64 and 18; and for all ages of childhood tuberculosis exceeds whooping cough by an inconsequential margin, 6.9 and 6.6 per 100,000, age specific rates. Of all infections, only the pneumonias and the diarrheas and dysunder 5, except for the Netherlands and Switzerland where diphtheria heads the list[160b].

Morbidity. Because of the stated limitations inherent in reported cases, current behavior of these diseases as a group is illustrated by data of a selected community where reporting has been long practiced and is well established. The information provided by Massachusetts serves the purpose. For the 10-year period, 1940 to 49, the mean annual values for reported cases and rates for total population are set forth in Table 2.

Whooping cough ranks fifth in frequency of reported cases. Using the method of Feemster[44], to whom we are indebted for many of the data here presented, in order to judge completeness of reporting, cases of whooping cough notified in Massachusetts represent 18% of infections that actually occur. That is also the precise figure determined by field survey in Maryland[148].

EPIDEMIOLOGICAL TRENDS IN WHOOPING COUGH IN THE UNITED STATES. For more than 50 years, death rates from whooping cough have consistently declined. During the first quarter century the gain was satisfying but not great. After 1925, progress accelerated so that today deaths from pertussis are 6.6% of what they were in 1900. These general observations, based on data of the registration states of 1900, are reflected in the behavior of whooping cough in selected areas where reporting is especially satisfactory (Fig. 1). In New York City the death rate in 1900 was 16.9 per 100,000 population; in 1948 it was 0.1. Massachusetts had a rate of 12 in 1900 and 0.2 in 1950. A similar situation has prevailed in Great Britain[66], where the rates of 1921 to 1930 were a third of what they were in 1861 to 1870, and for 1945 to 1949, one-seventeenth[121]. The trend in Canada[97] has followed the same pattern.

In searching for the causes of such a generally more favorable situation, the first inclination is to look for an altered character of the infectious agent. No evidence exists of a lesser virulence; whooping cough, when it occurs, presents much the same clinical reaction as in years past.

Specific immunization is clearly not the determining factor in the long-term trend. The declining mortality was under way many years before vaccines were introduced, and the greater part of the gain was accomplished before they came into general use.

A third possibility is that fewer deaths from whooping cough occur now because there are fewer cases. The record of reported cases in all areas illustrated in Fig. 1 shows rather the opposite situation. Cases had increased, remained stationary and then showed a tendency to decrease somewhat, while deaths consistently decreased. The recorded increase in cases is probably the result of improved reporting, with the true state of affairs that the frequency

TABLE 2. ACUTE COMMUNICABLE DISEASES OF CHILDHOOD. MEAN ANNUAL REPORTED CASES, AND RATES PER 100,000 POPULATION, MASSACHUSETTS, 1940 TO 1949.

Disease	*Mean Annual Cases*	*Mean Annual Rates Per 100,000 Population*
Whooping cough	6,623	152
Chicken pox	15,130	342
Rubella	5,946	135
Mumps	10,792	242
Measles	24,599	552
Diphtheria	248	6
Scarlet fever	8,426	190
Poliomyelitis	416	9
Meningitis	197	5

Source: Department of Public Health, Commonwealth of Massachusetts, Division of Preventable Diseases.

of whooping cough remained unchanged. The experience of the past 5 years, and to an extent of the past 10 years, differs sufficiently from the earlier trend to raise the question of a turn of events. The principal new factor introduced during this period was a material increase in immunization against whooping cough. A number of factors brought this about, among them the development of better immunizing materials, an increased interest in preventive medicine after the war years, a solid endorsement of whooping cough immunization by pediatricians and the American Medical Association Council on Pharmacy and Chemistry[45a] and perhaps most important of all, the ease with which whooping cough protection could be included along with diphtheria and tetanus by way of the new triple vaccines. The validity of increased immunization in partial explanation of the falling attack rates could be tested by comparing the experience of Seattle and other cities where immunization has been emphasized, with comparable cities having no general immunization program.

The medical profession of Seattle has been especially active in promoting whooping cough immunization. A field survey[70] in 1949 showed 69% of children immunized against whooping cough by age 2 in King county. Immunization was more general in the city of Seattle, and an estimate of 74% immunized was made for the city. Reported cases in Seattle by 5-year periods, beginning in 1930, were 286, 170, 174 and 56 for 1945 to 1949 per 100,000 population. Cases showed a well marked shift toward an older age of attack. There were no deaths in thi

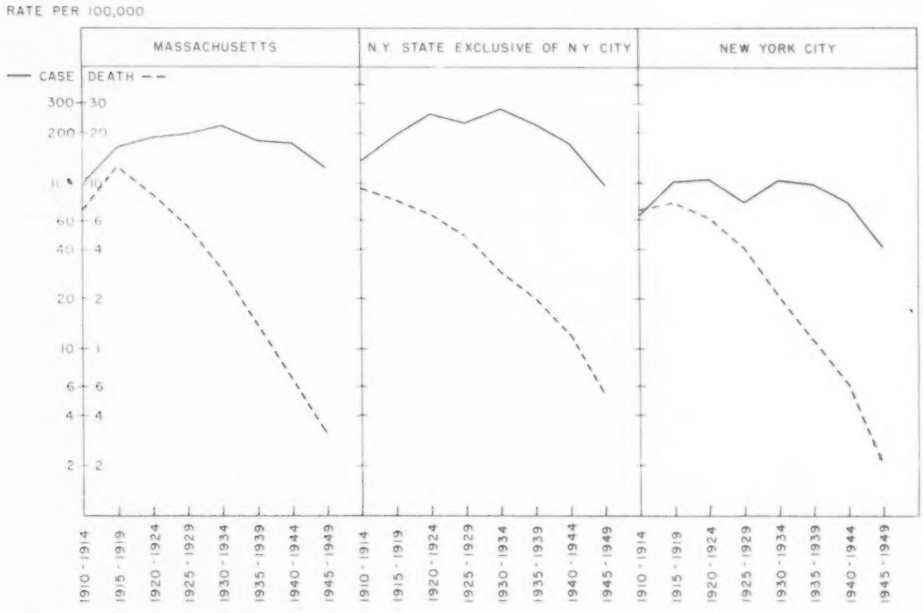

FIG. 1.—Whooping Cough, reported cases and deaths per 100,000 population, Massachusetts, New York State (exclusive of New York City), and New York City, 1910 to 1949.

city of 464,853 population in 4 of the 5 last years of this experience, an unprecedented circumstance in records that go back to 1900.

Still another possibility is that the recorded decline in deaths is artificial and not real; that deaths formerly reported as whooping cough are now assigned to some other disease, of which pneumonia is the most likely. No regulation or ruling of constituted authority is known to have been responsible, although that mechanism has induced changes of similar moment. Dauer[31] explored the alternate possibility, that custom is responsible, but eliminated that consideration by proof that during the same period and at ages usual for whooping cough, deaths from bronchopneumonia had declined in equal degree with those for pertussis. The answer to the remarkable decrease in deaths from pertussis over this long period would seem to rest in a lesser case fatality.

Reliable data on case fatality are among the more difficult to obtain in epidemiology. Emerson[41a] reports as of 1937 case fatalities for cities over 500,000 population that varied from 0.7% to 4.3%. Data on isolated epidemics are to be had, such as 1.1%[83] for whooping cough in a foundling home and the series of endemic cases reported by Sako[127] with a rate 0.76%. What is needed is information to demonstrate a trend over a period of years, comparable to the observed data on mortality. Hospital information is biased and notably open to error through changes in admission policy or other administrative procedure. The whooping cough records of the Herman Kiefer Hospital in Detroit have more than usual value because they represent a 25-year experience under a continuing system of records and a fixed policy of admitting only severely ill patients or those with complications. A progressive and noteworthy improvement in case fatality is evident (Table 3). For patients under 1 year of age, fatality decreased from 42.3% in 1927 to 3.3% for the 211 cases of 1950.

Another source of information is the ratio of reported cases to deaths in a community. This gives a case fatality of variable worth, depending on comparable completeness in reporting cases and deaths. The consistently reliable data of the Providence, Rhode Island, health department (Table 4) show a lesser case fatality over the years, roughly proportional to the declining mortality rate.

The reasons for the decline in case fatality, seemingly the principal factor in the better mortality rates, are now sought. Conceivably the answer rests either in an improved method of treatment, in a change in constitution of the herd to give a mass host with greater resistance, an altered agent, or finally, in environmental factors that enhance the resistance of the host or limit activity of the infectious agent. The evidence and discussion that follow are directed to that end.

THE CLINICAL DISEASE. This review is primarily concerned with whooping cough as a mass disease of the community or herd. Epidemiologists of experience appreciate, however, that the point of departure in study of any mass disease is to know the clinical behavior at the bedside.

Viewed clinically, whooping cough is also a paradoxical disease. The acute febrile illness is not to be identified by clinical means, for the reaction in the catarrhal stage is that of a number of other mild respiratory infections. A history of exposure may suggest its nature, and confirmation may be had bacteriologically, but clinical recognition comes when the acute process is over, and with communicability greatly decreased. The paroxysmal nature of

the cough and finally the whoop mark the disease as truly whooping cough, but the fever has then subsided and the process is not the acute infection of pertussis. Four stages characterize the classical disease: the period of incubation, the catarrhal episode, the paroxysmal stage and convalescence.

The incubation period has an attraction for the epidemiologist, as the means by which to trace the source and course of an infection as it passes through a community. A regularly occurring period favors case finding, while marked irregularity limits accomplishment. Allowing for difficulties in recognizing the first signs of an upper respiratory infection, the incubation period of pertussis is thoroughly regular, commonly 7 days and almost uniformly within 10 days. In 2 instances of experimentally induced whooping cough in children[91] the incubation period was 7 days. Shorter periods of 5 days are repeatedly observed in family outbreaks, but the 3-day intervals recorded by Stocks[143] are not borne out by field experience. The value of 15.4±1.3 days[72] is believed inordinately long, and the limit of 21 days is surely rare.

The catarrhal stage resembles an ordinary upper respiratory infection with somewhat more than the expected amount of cough. Fever is usually present, of low grade but sometimes passing 101° during the first few days. The catarrhal stage lasts from 1 to 2 weeks and usually passes into the paroxysmal stage. Early recognition of that event may be aided by tracheal compression which often serves to induce the typical paroxysm.

TABLE 3.—WHOOPING COUGH, CASES AND CASE FATALITY, HERMAN KIEFER HOSPITAL, DETROIT, 1927 TO 1950

Years	*Age in Years*							
	0–1		*1–4*		*5–9*		*All Ages*	
	Cases	*Case Fatality*	*Cases*	*Case Fatality*	*Cases*	*Case Fatality*	*Cases*	*Case Fatality*
1927–29	53	42.3	120	19.2	34	2.9	207	22.2
1930–34	178	39.3	267	14.2	89	4.5	541	20.7
1935–39	268	19.4	360	12.2	90	3.3	724	13.7
1940–44	252	16.7	243	5.8	72	2.8	571	10.2
1945–49	512	5.8	295	2.7	59	0	872	4.4
1950	211	3.3	89	2.2	19	5.3	323	3.1
Total	1476	15.11	1374	9.4	363	3.0	3238	11.2

Source: Herman Kiefer Hospital, Division of Communicable Diseases, Detroit.

TABLE 4.—WHOOPING COUGH, REPORTED CASES AND DEATHS, PROVIDENCE, RHODE ISLAND, 1930 TO 1950

Years	*Cases*	*Deaths*	*Case Fatality*
1930–34	3679	50	1.36
1935–39	4990	31	0.62
1940–43	4057	15	0.37
1945–49	3708	9	0.24
1950	1803	0	—

Source: Annual Reports of the Superintendent of Health, Providence, Rhode Island.

The paroxysmal stage is the significant part of the disease, although the manifestations of an acute infection are largely past and the patient afebrile. Cough is the distinctive feature, and characteristic of no other disease; so much so that clinical diagnosis has no difficulties. To those who appreciate the opportunities provided by simple diseases we commend Pospischill[118] and his clinical observations on more than 25,000 cases of whooping cough. The duration of the paroxysmal stage is extremely variable, commonly 4 to 6 weeks, and with limits of 2 to 20 weeks. Communicability is less but nevertheless persists for 2 or 3 weeks.

Certain related clinical features of whooping cough have a direct bearing on epidemiological interests. The initial process is that of a local lesion of the nasopharynx, larynx and bronchial tree, a superficial infection of respiratory mucous membrane[53,101]. Extension occurs through the bronchi and bronchioles[130] and to the alveoli[137]. The surface location of the early lesion should have the same epidemiological significance as in influenza. Whooping cough should be a readily communicable disease. It is believed to be so and beyond usual conception. A further consideration related to pathology is that death in whooping cough is uncommonly by means of the disease itself but more often as the result of secondary infection with a complicating bronchopneumonia.

Whooping cough is subject to many gradations of severity. Not all patients whoop. Patients whoop without pertussis. Atypical attacks of short duration are not uncommon, being attended with little constitutional reaction and no whoop or only an occasional mild paroxysm. The clinical reaction is sometimes abortive, no more than a simple bronchitis lasting a few days and yet capable of bacteriological confirmation. Smith[138] followed an outbreak in a school where only 20% of patients had a characteristic whoop. Such attacks presumably occur in elderly persons more often than is recognized, but the aged also have typical disease. Absence of the characteristic whoop is no mark of a mild infection, for young infants are known to suffer severe and even fatal illness with no indication of whoop.

Infection with *H. pertussis* ordinarily results in frank symptoms and classical manifestations. Evidence yet to be presented suggests the rare occurrence of inapparent infection, as occurs in diphtheria and a number of other diseases. The point to be made now is that atypical and yet clinically definite disease, frequently not recognized as pertussis, is a considerable part of the composite of whooping cough as it affects populations. Several pieces of epidemiological evidence enter into the proof: the survey data of Collins[24] that 73.5% of children give history of whooping cough by age 17 years, the finding of Thompson[149b] that 30% of children without history of pertussis react to skin test, and finally the observed secondary attack rates of about 80% for presumed susceptible children, 20% escaping[129c]. The proportion of abortive and atypical cases is believed to be in the nature of a fourth of the total.

A final consideration is that not all cases of "whooping cough" are specific infections with *H. pertussis*, which leads some to prefer the name pertussis to the old-fashioned term. That seems an unnecessary nicety, provided one knows infectious disease. Another disease, parapertussis caused by *H. parapertussis*[40a], so resembles mild pertussis clinically as to be indistinguishable except by laboratory means. An attack by one does not protect against the other. *H. parapertussis* is widespread, having been identified in a

number of states from California[109] to Philadelphia[50], and in Mexico. The infection presumably is often overlooked because of the mildness of the clinical disease; it may well be a confusing factor in epidemiological studies of pertussis, and assuredly has caused independent outbreaks[9a]. Other clinical conditions also resemble whooping cough.

Epidemiological Attributes of Whooping Cough

With epidemiology interpreted as medical ecology[60] and with mass disease a phenomenon of multiple causation, the analysis of whooping cough as a disease of communities is developed conveniently in terms of the ecologic triad which determines origin and course, which is to say according to the infectious agent, the host as a herd, and the complex environment[59].

THE INFECTIOUS AGENT. A clear definition of the responsible infectious agent is of material aid in the development of rational control measures in operational epidemiology. It is also the theoretical basis for specific immunization. Practical relationships to field activities include the contribution of microbiological methods to clinical diagnosis, an understanding of pathogenesis of the individual disease, and a knowledge of reservoirs of infection.

A small bacillus, *H. pertussis*, was first observed and cultured from the sputum of an infant with whooping cough by Bordet and Gengou[8] in 1906. For many years this microorganism, the causative agent of pertussis, was accepted without question. In modern times, three problems have concerned epidemiologists.

Although *H. pertussis* was clearly a regular feature of clinical whooping cough, a virus was suggested[89,90,122] as having a dual relationship in causation of the disease, an hypothesis also entertained at that time for scarlet fever. Support for a single bacterial origin[78,99] of pertussis was promptly forthcoming. A virus was never demonstrated, and *H. pertussis* served of itself to produce the disease in man[91] and in experimental animals[123,146].

The demonstration that whooping cough bacilli dissociate in the course of artificial cultivation had an important bearing on preparation of whooping cough vaccines. A single antigenic type characterizes strains on primary isolation from lesions[22,133]. On further cultivation the organism dissociates through 4 phases[85], gradually losing virulence and undergoing marked changes in antigenic structure. The demonstrated need of virulent S-form phase-1 organisms in preparation of an efficient vaccine had the effect of settling much of the controversy on the immunizing value of pertussis antigens.

A third problem was the possible existence in nature of different strains or types of *H. pertussis*. None has been demonstrated. This line of investigation led, however, to identification by Eldering and Kendrick[14a,40a,40b] of a related species, *H. parapertussis*, which has common antigenic fractions with *H. pertussis*, and *Brucella bronchisepticus*[17], and yet is not identical with either. Major and minor specific antigens were later identified[50] with demonstration that the minor component was responsible for the cross reactions. *H. parapertussis* gives pulmonary lesions in mice[39] resembling those of experimental murine pertussis. The epidemiological implications are evident but largely unexplored.

Diagnosis. The nature of early clinical whooping cough and the frequent atypical course without whoop make laboratory aids to diagnosis a necessary feature in early pertussis and often an essential in definitive recognition of

later cases. The cough plate[20] has proved a useful measure for clinical purposes[35] but never has been wholly satisfactory in field practice. Nasopharyngeal swabs[14b] give results comparable to the cough plate[27a]. Some workers[15,126] prefer dual cultures by both methods and others believe the swab superior. The method is suited to epidemiological purposes in field study, especially the modification using penicillin[12]. Demonstration of humoral antibodies is of little practical value in diagnosis, for they do not appear until the third week.

Pathogenesis. The pathogenesis of whooping cough is ill-defined. The enduring immunity after attack is scarcely compatible with a purely local infection of the upper respiratory tract. If that were the case, pertussis should behave more like influenza. Since immunity is demonstrably long-lasting, its origin may be postulated as depending on one of three mechanisms. There may be a general bacteremia. *H. pertussis* is not regularly recoverable from the blood, and there is doubt that it ever has been so demonstrated[159]. The immunity conceivably could be due to an associated virus, but that again has been rather well eliminated. There remains the hypothesis, clearly unsupported, of a general distribution of a locally formed toxin.

The lesions of the upper respiratory tract in late whooping cough have little to indicate a chronic infection of the mucous membranes. The long duration of the disease suggests a descending infection and this is rather well-established[159]. Wide differences of opinion exist as to the cause of the pathologic changes of the lungs, whether they are due to pertussis bacilli or to secondary invaders. Evidence exists for a simple uncomplicated form of whooping cough, for a descending specific infection of the lungs, and for a complicated form due to pneumococci, streptococci, or other infectious agents. Epidemiological correlation between a prevailing acute respiratory infection and an increased incidence of pneumonia after whooping cough is no uncommon observation. The responsible mechanism in postpertussis encephalitis is unknown.

Reservoirs of Infection. Man is the only known source of pertussis infection. Other than the patient with frank whooping cough, who is a regular and highly active source of infection, the question of reservoirs resolves into whether or not carriers exist, and secondly the frequency of atypical and abortive disease.

The carrier state needs definition. Transient, accidental implantation of an infectious agent without penetration of tissue may occur but has little epidemiological significance. The numbers are too small and persistence is too brief. This is the true healthy carrier. Carriers to be of importance are one of 3 kinds; the incubationary carrier, the convalescent carrier who still maintains a focus of infection after clinical recovery, and finally the individual never presenting clinical manifestations but having an inapparent infection. The latter is the usually termed healthy carrier, but the state of infection without clinical disease is to be recognized by bacteriological and serological means. Without penetration of tissue and consequent food supply, the agent is not maintained. What is the situation in respect to whooping cough?

Kline[76] reviews the carrier situation in whooping cough. He records 4 healthy contacts to pertussis with demonstration of 1 colony per plate and no mention of identifying the organism as *H. pertussis*. Blatt *et al.*[7] isolated whooping cough bacilli from 3 persons who had never had pertussis and from 3 others with pertussis 3 years previ-

ously. Other workers with much experience have never identified carriers among contacts[78,158,135]. Chronic carriers after clinical attack have been recorded twice[55,144]. The conclusion is that the healthy carrier state may have been identified on occasion, that carriers by way of inapparent infection are rare, and that the chronic convalescent carrier is a curiosity. Improved bacteriological methods may well enlarge this meager experience and prove carriers somewhat more common, but the inference is justified that carriers are of little consequence in the epidemiology of whooping cough.

Abortive infections with symptoms simulating simple respiratory infection of a few days' duration, and the atypical case with more severe reaction are another matter. They are among the more active sources of infection, because they are unrecognized and because the patients commonly continue their usual activities. These are the missed cases which enter into all epidemiological practice. Numerically they are not without consequence. An estimate based on experience is that abortive cases constitute from 3 to 5% of total pertussis disease, and unrecognized atypical cases a good 20%. Casual data from field studies support the estimate.

Host Factor. The host factor in mass disease finds a ready division into those features of resistance that are an innate part of man as an organism, termed inherent insusceptibility or autarcesis; and secondly, the immunity acquired through specific antibodies, artificially produced or resulting from natural contact with the infectious agent. A goodly part of the explanation for the changing character of whooping cough as a mass disease, already broadly noted, is to be found in an absolute and proportional reduction in physically substandard children[97]. Better nutrition, the aging of the American population, the decreasing size of families, and a falling birth rate[41b] are among the factors that set in motion a decline in deaths which has continued despite more births and a larger child population in the post-war years. A uniformly satisfactory evaluation of the various host factors is impossible. Some have not been studied at all and only impression exists, for instance the relation of cases of whooping cough to numbers of undernourished, scorbutic and rachitic children. The cardinal features of age, sex, and race are well understood.

Age. A singular feature of whooping cough, compared with other infections of childhood, is the marked predilection for attack of infants and young children. No age is exempt from pertussis, but most humans have the disease early in life. So many adult patients give a history of previous attack as to suggest that late primary infections are most unusual. Data on whooping cough in military practice, to be introduced later, support that view. Table 5 gives the percentage distribution of cases of whooping cough in Massachusetts by ages, for 3 selected periods. For the current period more than 47% of cases are within the first 5 years of life, and rather evenly distributed. The value for the early years was 55%. Cases beyond 10 years are always few. Comparison of the 3 series brings out the important observation that a shift in age of attack has occurred, from a maximum level at age 3 in 1918 to 1921 to 6 years in 1945 to 1949. A changing character of the population is suggested; immunization may be a factor.

The distributions cited for Massachusetts do not hold for the country as a whole, for like the other communicable diseases[43], whooping cough is a

relatively more frequent disease of children under 5 years in the southern states than in the north. The proportion under 1 year is also greater, as illustrated by the experience in Alabama[31]. Despite fairly wide differences in age distribution from state to state and even in contiguous states, a trend has developed in the past 25 years toward a field surveys in 1928 to 1931, when whooping cough was found to attain a maximum incidence at 3 years; measles had a double peak, one at 2 years and again at 5 and 6 years; and chickenpox, mumps, scarlet fever and diphtheria had a characteristically low incidence in the earlier years with a sharper peak at ages 6 and 7.

TABLE 5. PERCENTAGE DISTRIBUTION OF CASES OF WHOOPING COUGH BY AGE GROUPS IN MASSACHUSETTS, 1918 TO 1949

	Age in Years													
Years	*Under 1*	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*0–4*	*5–9*	*10–14*	*15 & Over*
1918–21	10.3	10.3	11.2	11.9	11.2	11.5	11.6	7.1	4.7	2.8	54.9	38.5	4.0	2.2
1935–39	7.5	8.4	10.0	11.1	11.6	12.9	14.9	9.9	5.5	2.8	48.6	46.0	4.1	0.9
1945–49	8.9	7.2	9.9	10.4	10.7	12.3	13.5	9.6	6.5	3.7	47.1	45.5	5.5	1.9

Source: Department of Public Health, Commonwealth of Massachusetts, Division of Communicable Diseases.

TABLE 6. DEATHS FROM WHOOPING COUGH, MASSACHUSETTS, 1945 TO 1949, BY AGE IN MONTHS AND YEARS.

	Age	*Number*	*Percent*
Months	0–3	11	15.5
	4–6	12	16.9
	7–9	8	11.3
	10–12	12	16.9
Years	0–1	43	60.6
	1	13	18.3
	2	5	7.0
	3	5	7.0
	4	1	1.4
Five yr.	0–4	67	87.3
	5–9	3	4.2
	10–14	1	1.4
All Ages		71	100

Source: Department of Public Health, Commonwealth of Massachusetts, Division of Preventable Diseases.

more advanced age of attack. Another factor in the lesser death rates of today is thus identified, for deaths at age 6 are far less frequent than at age 3.

In comparison with other acute communicable diseases of childhood and for the country as a whole, the peak in age incidence of whooping cough is still earlier than any other. Collins[24] established that relationship through

Death rates for whooping cough are higher in the first year of life than at any other age, again a unique feature among common communicable diseases. That behavior has held for at least 200 years[66]. An exaggerated frequency of deaths continues through the second year. Beyond the third year whooping cough is of little moment. Recent experience in Massachusetts, as

presented in Table 6, illustrates this point; and it has been amply established in earlier years and by many workers[57,70,88,129b]. The extreme significance of whooping cough in the first year of life is seen, in that 61% of all deaths are under 1 year, and 32% under 6 months. The peak mortality for the United States generally, is in the second, third and fourth months of life[104].

For the country as a whole, deaths under 1 year have increased proportionately since 1900. Of 37,774 cases observed in Milwaukee[52] from 1933 to 1948, 7.9% of cases were under 1 year of age but they contributed 72.4% of deaths. For the last 8 years the proportion is 79.4%. The same phenomenon is illustrated in deaths from whooping cough in Massachusetts (Fig. 2) from 1920 to 1949. The shift in age for deaths is opposite to that just noted for cases.

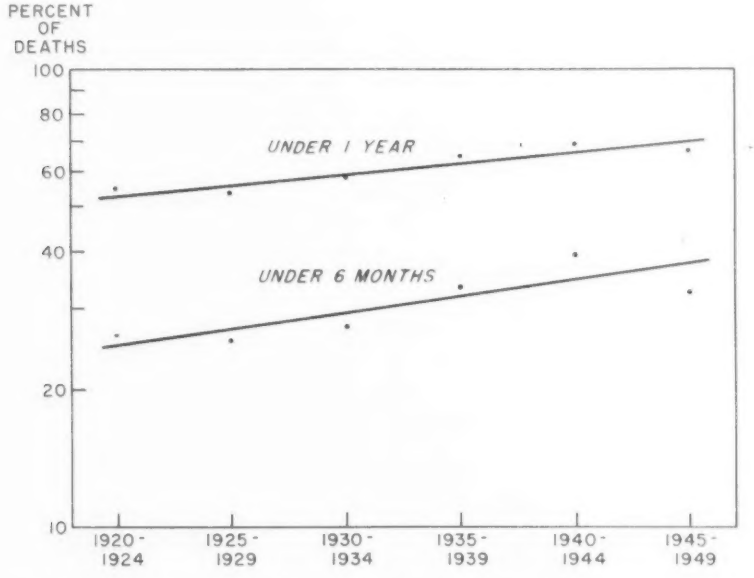

FIG. 2.—Deaths from whooping cough, % of total deaths occurring under 1 year and under 6 months, Massachusetts, 1920 to 1949.

The proportional increase in deaths from whooping cough under 1 year while mortality rates have been falling presents much the same situation as in general infant mortality, where total rates have fallen but neonatal deaths have shown less improvement and thus are brought into greater relative prominence. The practical value of centering attention on whooping cough at ages under 2 years, and especially under 6 months, is demonstrated.

Sex. No other single feature of the epidemiology of whooping cough is more anomalous than the sex distributions, both of cases and of deaths. Attack rates and mortality rates of females exceed those for males. This observation is of long-standing and it holds all over the world[32,100], for various races, in urban and rural areas, for primary and secondary cases of families, and during years of high and low

incidence[66]. Recent experience for white and non-white populations in Massachusetts is presented in Fig. 3.

After correcting for changes in sex ratios with age in populations at risk, Stocks[143] found that the differences were not only constant but they increased with age, so that the excess of females over males was 5% up to 4 years of age, 20% at the 8th year, and 50% by the 10th year. Differences in liability to attack appear to account for the differences in mortality, but a greater case fatality may have some part, as indicated by Madsen's[100] data, where females provided more cases but still more deaths, mortality being out of proportion to morbidity.

Disproportionate differences in sex distribution are seen in a number of infectious diseases, such as the male preponderance in brucellosis and tularemia, but these are explained on the basis of occupation or other function of the social environment. All other common communicable diseases of childhood except whooping cough are characterized by an excess of

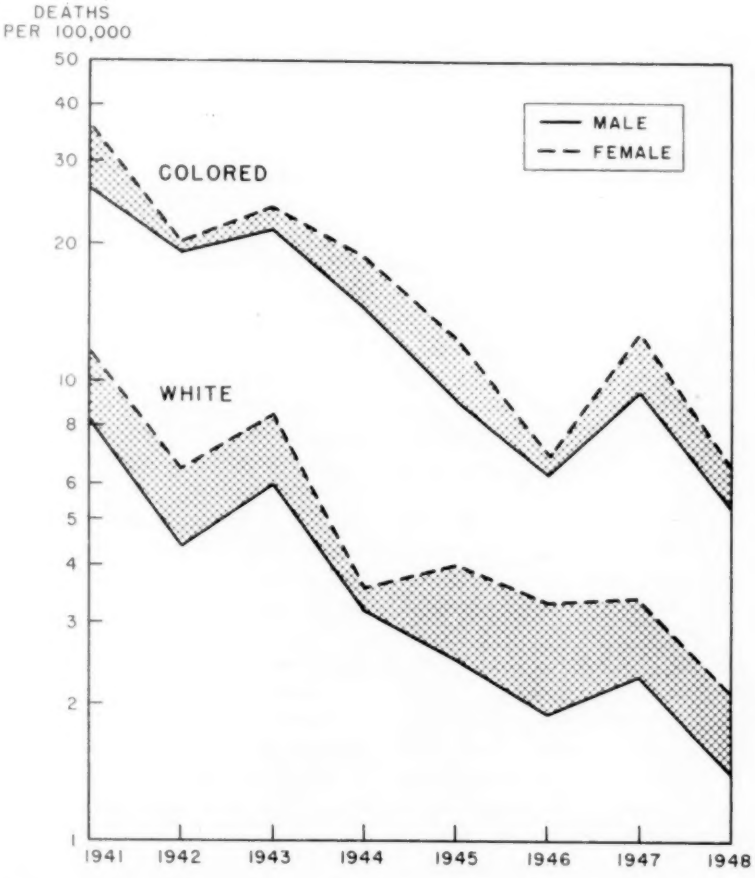

FIG. 3—Deaths from whooping cough by sex and color, Massachusetts, 1941 to 1948.

males. The explanation for the inverse ratio in whooping cough is indeterminate. Because of the uniformity with which it occurs under many conditions, the answer should rest in an undetermined host factor. The suggestion that the cause is to be found in the smaller larynx of the female scarcely holds, for Hill[66] points out that up to age 6 the sexes show no difference in size of larynx, and furthermore that males have the higher mortality with laryngitis and croup. The closer contact of adolescent girls with children may be a factor at those ages, but does not explain the similar behavior of infants. So far as the evidence goes, the explanation of Stark[141] in 1856 is about as good as any, when he states that "the causes of the greater hability of the female to death from whooping cough would appear to be produced by the greater tendency which the female sex exhibits to have fits or convulsions when attacked by a paroxysm of coughing".

Race. The races and nationalities of man are equally susceptible to whooping cough and thus in the United States attack rates are much the same for the white population and for Negroes, Indian, Chinese and others. Mortality rates are another matter (Fig. 3). Crum[28] 35 years ago found the death rate for Negro children under 1 year to be 3 times as high as for white children of the same age, and for the age group, 1 to 4 years, it was 5 times greater. Conditions have not changed, for our analysis of white and non-white populations of the registration area for the years 1941 to 1948 shows ratios to range from 3 or 4 to 1, at different ages and in various years. Indians have rates about 6 times those for whites, while rates in Chinese and Japanese approximate the white rate[31].

The causes of the excess frequency of death in non-white populations are not because of a greater frequency of cases. The greater case fatality would appear broadly attributable to variation in social environment and a resulting host constitution not so resistant to pertussis infection.

Immunity. The recorded frequency of whooping cough at such early ages as a week to 2 months is evidence that maternally transferred passive protection is low-grade compared to other common communicable diseases of childhood, for example, diphtheria and measles. The high secondary attack rate in families proves that susceptibility exists until whooping cough appears, and that immunity is from clinical attack rather than inapparent infection. Probably 95% of persons have pertussis in classical or atypical form some time during life. The lack of naturally acquired immunity other than by attack is also evidenced by populations where whooping cough has long been absent. Exposed to the infection, old and young acquire the disease, as in the Faroe island epidemics[100]. In the St. Kilda island outbreak[140] whooping cough had been absent for 29 years, and no one older than 29 years got the disease and no one younger escaped, except a former resident of Glasgow.

Intrauterine infection has been suggested by an infant 1 day old, born of a mother with whooping cough[124], and by a few other scattered case reports[21,56,105]. The more usual and probably more accurate observation is the appearance of whooping cough in the newborn within a reasonable incubation period, 3 to 8 days after birth[33,111,117].

Too many young infants get the disease, and too many die, for passive protection of maternal origin to be much of a factor in resistance. Tests of maternal and cord blood[155] demonstrate that antibodies against *H. per-*

tussis[111] are so transmitted[23a]. That antibodies constitute a protective mechanism would appear to be established by the protection afforded children by immune rabbit serums[13]. That the concentration of antibodies in maternal blood is sufficient for practical protection is not so clear. Lichty[87] reports death rates for whooping cough of infants under 6 months as higher when mothers had not had whooping cough, with little correlation for deaths after 6 months. The suggestion is of placental transfer of passive immunity. The practical suggestion followed[12d, 23b, 74] of hyperimmunizing mothers during pregnancy. Although normal passive immunity appears negligible, a satisfactory protection might be developed artificially[1]. The practicability and efficiency of this procedure are yet to be demonstrated by adequate field trial. However, absence of infant immunity is another instance of the anomalous epidemiology of whooping cough.

Duration of immunity after clinical attack is prolonged and usually permanent, but not wholly so. No circulating antibody is present to account for the usual lasting immunity, since protective substances tend to disappear within months after attack.

In a comprehensive study of 20,405 cases, Laing and Hay[81] determined second attacks of whooping cough to occur in the proportion of 0.26%. As with pertussis generally, second attack was more often noted among females than males. Bacteriologically proved instances of both first and second attack are rare, but that is a severe requirement to demand of any disease. The usual circumstance in second attacks has to do with an adult exposed to familial infection. The newly developed knowledge of parapertussis suggests that some instances, presumed to be representative of second attack, are in reality instances of another kind of infectious disease.

A means of measuring immunity in whooping cough has practical application first as a diagnostic aid in early, atypical, or late infections that are bacteriologically negative; in field surveys for epidemiological purposes; and finally, to assay potency of whooping cough vaccines. No entirely satisfactory method exists. *In vitro* antibody tests, which include complement fixation, agglutination, and opsonocytophagic tests, are not sharp[46,47]. The new antihemagglutinin test has promise[75]. The mouse protection test finds its principal use in biologic assay of vaccines[73].

Two types of skin test material have been used, a heat labile toxin[49,145], and an agglutinogen[140], with the latter apparently having more merit. Field use of the agglutinogen test in epidemics[46,47] indicated a considerable degree of reliability, in that secondary cases occurred only in children whose skin tests indicated susceptibility or weak immunity. The test shows good correlation with *in vitro* tests for antibodies[131]. It has been used also in evaluating potency of immunizing material[4] and the results of vaccination against pertussis[108]. Thompson[149a,b] used a skin test which he considered as allergic in character and a function of endotoxin. Children with a history of whooping cough reacted to the test in a proportion of 85%, and individuals without a history, to the extent of 30%, which was interpreted as a measure of the extent of latent immunization. The results from clinical use of skin testing in whooping cough are such as to warrant comprehensive field trial to establish the general epidemiological value of the procedure.

ENVIRONMENT. Indication has already been given that the principal reasons for the improved case fatality

of whooping cough are to be found in changes in the mass host, and that environment has had a prominent part in bringing that about.

Physical Environment. Seasonal variations in incidence are less pronounced in whooping cough than for the other diseases of the childhood group. The high level of sub-epidemicity, so characteristic a feature of the disease[18], is expressed in most cities of appreciable size by a continuing presence of pertussis at all seasons[100]. Such seasonal peaks as may be determined are of low amplitude[63a] and do not fall into consistent geographical groups based upon climatic conditions[63b]. General differences do exist, in that maximal seasonal incidence tends to occur late, about May, in southern and Pacific states and earlier, in January to March, in northern states. The relation of these high points to one another is the reverse[63a] of what has been found for such other respiratory infections as diphtheria, scarlet fever and measles. During periods of low prevalence, the seasonal distribution of whooping cough exhibits less amplitude than during high prevalence, but the rise is always more a plateau than a peak, long continued, and even in northern states often extending into May or June and sometimes August[65]. Whooping cough is thus characterized among the common communicable diseases of childhood by an absence of prominent seasonal incidence, by irregularity in the peaks that occur, and by the frequency with which seasonal excess extends into late spring and summer.

The present century has seen a progressive shift in the distribution of the common communicable diseases of childhood from an urban to a rural distribution, as judged by deaths. Whooping cough was the first of the group, in 1910, to show higher death rates in villages and rural areas[57] than in metropolitan centers. That behavior is now well established[157a,b,c], and for the United States as a whole, counties with the highest death rates are consistently rural[31]. Morbidity in general parallels mortality.

Whooping cough is universal. It is found in the whole of the habitable globe, in temperate regions and in the tropics, although it is less common and less severe in warmer regions. Severity of climate has an influence on deaths[28] through a greater frequency of the pneumonias, but climate as a factor in type of disease and degree of spread is of secondary importance, although there are exceptions such as Ceylon, Chile, Jamaica, and the Scandinavian countries. La Paz, Bolivia, is a noted center for whooping cough with its extreme altitude, light rain and cool climate.

Biological Environment. Arthropods are not involved in the transmission of whooping cough nor are there natural animal reservoirs of the disease. A number of animals can be experimentally infected with whooping cough bacilli[9a,10].

Social Environment. Haven Emerson[41b] has included among significant factors in improved mortality from whooping cough such features of the social environment as better home hygiene and better home care of children. Dauer[31] found a fairly high degree of correlation between the percentage of illiterates over 21 years and the death rate from whooping cough. Families with 3 or more children under 10 years had high death rates, and strong correlation was established between deaths from pertussis and crowding, as judged by more than 1.5 persons per room.

The social environment is believed among the important factors that determine the behavior of whooping cough and many other diseases, but

opinion as to its actual significance rests largely on impression and not facts. The social environment is one of the least explored fields in the epidemiology of whooping cough, especially where the family serves as the unit of study. Such problems present as the relation of medical care to deaths, the effect of social status on liability to mixed infection and complicating pneumonia[161], and the reciprocal action of whooping cough and other mass disease, for instance tuberculosis[150]. The opposite endeavor, to use *H. pertussis* or other highly communicable infectious agent as a tracer element in determining social phenomena, is suggestively an equally rewarding line of investigation. For the better examples of the social environment as it acts in whooping cough, recourse is had to the broad international scheme and to the results of wars.

Before the recent world war, Iceland was a relatively isolated island country. The course of events with whooping cough was an epidemic about once every 7 years and lasting from 6 to 12 months[36]. Having burnt itself out through exhaustion of susceptibles, whooping cough disappeared until enough time had elapsed for a new lot of susceptibles to have been born and again a chance importation of the infectious agent (Table 7). In 1941, Iceland became a center of war activity. The immediate effect was an increase in all communicable disease—and extensive epidemics of the common contagions of childhood, including whooping cough. After the war, Iceland became a busy crossroad in transatlantic traffic, with the result that the epidemiological pattern of the common communicable diseases of childhood has changed from cyclic outbreaks with intermediate freedom from infection, to an established endemicity and presumably no more great epidemics. The difference in behavior of

TABLE 7. ANNUAL INCIDENCE OF COMMON COMMUNICABLE DISEASES IN ICELAND, 1928 TO 1950

Year	*Diphtheria*	*Scarlet Fever*	*Typhoid Fever*	*Measles*	*Mumps*	*Whooping Cough*
1928	17	14	49	2,293	0	258
1929	6	10	28	3,026	998	3
1930	9	204	23	0	1,858	10
1931	14	336	48	31	325	277
1932	10	624	65	132	4	0
1933	3	426	11	0	3	0
1934	1	900	19	0	2	0
1935	68	109	24	16	0	8,267
1936	68	70	9	8,245	16	88
1937	8	288	20	163	1	0
1938	—	197	3	1	1	0
1939	4	64	6	1	0	0
1940	4	33	3	14	1	0
1941	9	158	4	0	197	290
1942	11	321	5	1	5,034	4,413
1943	63	456	—	6,616	601	39
1944	1	261	4	540	13	7
1945	1	65	1	3	0	129
1946	3	22	1	23	4	1,556
1947	2	13	2	4,396	19	15
1948	2	193	0	377	397	0
1949	1	354	0	15	1,389	37
1950	0	61	0	516	634	166

Source: Professor J. Sigurjonsson, Reykjavik, Iceland.

diseases associated with inapparent infection and carriers and of those characterized by frank attack is nicely brought out. Diphtheria, scarlet fever and typhoid, introduced into Iceland, became firmly established and continued as endemic diseases until typhoid succumbed to an improved sanitation and diphtheria to immunization, scarlet fever continuing unchanged. Measles and whooping cough, and to a lesser extent mumps, came and went according to the chances that brought infection to the island. When war brought marked changes to the relationship of Iceland to the rest of the world, all diseases reacted promptly, but measles, mumps and whooping cough most profoundly.

The experience of the United States Army in the last 2 wars illustrates the influence of a changing social environment on the common communicable diseases of childhood, and particularly, of the altered rural–urban relationships as an index of the degree of implantation in the American population. Most recruits from urban areas may be expected to have had the common communicable diseases of childhood, those from rural areas to a lesser extent, with the result that the main problem in military practice is the rural recruit. The favorable circumstances of crowding and aggregation incident to military life bring on the common infections which the recruit has escaped as a child.

The data of Table 8 relate to troops in continental United States and bring out 2 things. The first is the materially lesser rates for all diseases in the second World War, suggesting a more thorough salting of the population with infection prior to the later date. The experience of the rural recruit more nearly approximated that of the recruit from the city.

The most striking difference, apparent in both series of observations, is the disproportionate frequency of the 5 common communicable diseases of childhood. Mumps, measles, and rubella all exceeded whooping cough by extreme margins and chickenpox appreciably. Whooping cough was the first of these diseases to establish a preponderance of rural attack. The few cases that occurred in military practice suggest that most recruits, both rural and urban, had had whooping cough prior to military service, and

TABLE 8.—CASES AND RATES PER 1000 POPULATION, U. S. ARMY IN CONTINENTAL UNITED STATES, WORLD WAR I, APRIL 1, 1917 TO DECEMBER 31, 1919 AND WORLD WAR II, JANUARY 1, 1942 TO JUNE 30, 1945.

	World War I		*World War II*	
Disease	*Cases*	*Rate Per 1000*	*Cases*	*Rate Per 1000*
Mumps	141,628	63.36	83,076	6.4
Measles	85,398	38.20	68,363	5.2
Rubella	16,167	7.23	96,892*	9.1
Scarlet Fever	9,038	4.04	26,824	2.0
Diphtheria	5,884	2.63	830	.06
Meningitis	2,878	1.29	10,502	.8
Chicken Pox	1,208	.54	8,366	.57
Whooping Cough	90	.04	153	.01

*Lacking 1942

Source: Med. Dept. of the U. S. in the World War, Vol. XV, Washington, D. C., 1925.
Division of Medical Statistics, Office of the Surgeon General, United States Army, Washington, D. C., Preliminary Data.

to a greater extent than for any other of these diseases. On this basis, whooping cough would be the most widely diffused of specific childhood infections. Support is also provided for the solid immunizing effect of a primary attack.

SPREAD OF THE INFECTIOUS AGENT. In continuing now the analysis of whooping cough as a biologic manifestation of disease in human populations, attention is turned from the part played by individual elements of the ecologic triad in origin of the process, to an examination of the course that whooping cough takes as a unit phenomenon affecting populations of people. The several considerations are grouped under communicability, period of infectiousness, and the endemic—epidemic patterns.

COMMUNICABILITY. Whooping cough is spread almost entirely by direct droplet transfer of infectious material from patient to susceptible contact. Indirect spread by contaminated objects must be relatively rare. No evidence exists on the importance of airborne transmission, but presumably it is of less importance than in measles.

The patient as a source of infection is predominantly the person who eventually has a paroxysmal cough. An appreciable number of patients, estimated at 25%, have atypical or abortive pertussis[72] and some few are early convalescents[100]. Subclinical and inapparent infections, with the persons affected acting as healthy carriers, are believed an unimportant factor; but systematic study of contacts, especially adult contacts with acute upper respiratory infection, is yet to be done by modern methods.

The regularity of exposure to known cases as the source of whooping cough infection is seen in the demonstrated efficiency of tracing sources of infection, 88% of 2,310 cases[88], in the high; 91%, secondary attack rates in families[6]; and in the nine-times greater frequency of whooping cough among susceptible children with known exposure compared with those not known to have had contact, the source in the latter group presumably including casual and unrecognized contact with patients and exposure to missed cases and to such carriers as may exist[72].

The high order of communicability has been repeatedly demonstrated by recorded secondary attack rates of susceptibles within families, with a range from 70%[33,151] in older experience, to a common 90%[71a,106b] with modern laboratory aids and survey methods, and to a full 100% in small intensively studied groups[29]. The rates are comparable to those of measles and chicken pox, diseases commonly placed ahead of whooping cough in communicability. Attack is furthermore prompt, for more than a half of secondary infections are within the first week of exposure[143]. As Hirsch[69] has expressed it, pertussis is "exquisitely communicable".

Exposure outside the home leads to lower attack rates, by 30% to 80% depending upon the kind of exposure, and emphasizes the greater effectiveness of intimate and repeated exposure, produces a lesser attack rate of susceptibles, from 25% to 50%[125], and reasonably so because of the dilution and spacing of susceptibles by those who have already had whooping cough (at that age somewhat more than half). The common circumstance is for the school epidemics to end promptly, with the outbreak continuing in the surrounding district as it progresses throughout the preschool population[143].

Period of Infectiousness. The height of infectivity is in the first week of the disease, during the catarrhal stage[84], a period in which Donald[35] in a large

series isolated *H. pertussis* from all patients, and subsequently in the second week 95%, third week 94%, fourth week 44% and fifth week 2%. The infectious agent has been demonstrated at least 2 days before the cough[76], and in a number of instances on the first day of cough[106a]. Infectivity wanes as the paroxysmal stage subsides[78] so that the pathogenic agent becomes difficult to demonstrate after the third week[30,55], and decidedly so after 4 weeks[135], although infectivity is known to have lasted for 8 weeks[84].

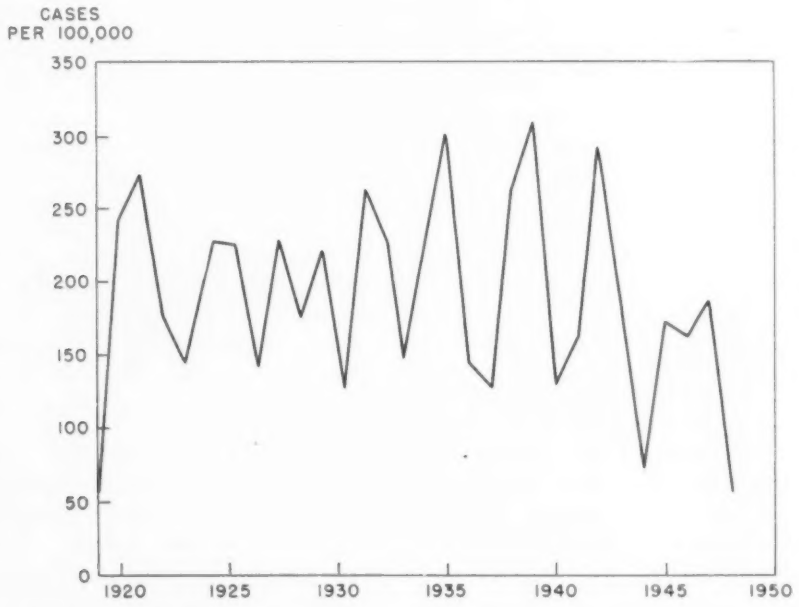

FIG. 4.—Whooping cough, reported cases per 100,000 population, New Jersey, 1919 to 1948.

THE EPIDEMIC WAVE. The fluctuations of whooping cough in populations are dependent upon the frequency with which infection is imported. The high order of infectiousness tends to exhaust susceptibles. Return of the disease depends on development of a new crop of susceptibles and reintroduction of infection. Where importation is frequent, where contagion is unbroken, as in metropolitan populations, periodic swings in incidence occur at intervals of 2 or 3 years. The lack of seasonal incidence suggests the promptness with which susceptibles of a population are attacked, provided chance produces the organism. The absence of pronounced epidemic years at appreciable intervals, so characteristic of mumps and rubella, is also evidence of this behavior. New Jersey experience is presented for the years 1919 to 1948 (Fig. 4), with the lesser incidence of the past 5 years as prominent a feature as in other areas illustrated.

When importation of the agent is infrequent, whooping cough burns out susceptibles and the disease disappears until the next reintroduction, a circumstance well illustrated by whooping cough in the Faroe islands[100].

From the beginning of the 19th century Iceland had much the same history (Table 7), with whooping cough irregularly introduced to produce great epidemics and then to disappear: epidemics that were not explosive, but spread by extension progressively and rapidly until susceptibles were exhausted.

SPECIFIC PREVENTION. The development of specific prevention of pertussis through active immunization by vaccines was mainly through studies by pediatricians, with a primary concern of these measures as a method of preventive medicine, directed towards protection of the individual rather than as a public health procedure. Inevitably epidemiologists were drawn to the field, first because the methods of epidemiology were needed to evaluate the procedure, and secondly because eventual demonstration of its worth justified the broader application as an activity of public health.

ACTIVE IMMUNIZATION. This most active field in the epidemiology of whooping cough has had attention earlier in this series of reviews[102] and on numerous other occasions[5a,27b,37,48,86]. For that reason, attention here will be limited to more recent contributions and to current opinion on issues yet open.

The well-nigh universality of the disease and the long-continued immunity after attack suggest immediately the practicability of artificial immunization against pertussis. The effectiveness of that measure is believed so proved, and is attested by competent authority. After a listing of 17 years in "New and Non-official Remedies", whooping cough vaccine was dropped in 1931 because of lack of evidence that it had any merit. It was reaccepted and endorsed by the Council on Pharmacy and Chemistry of the American Medical Association in 1944. The questions at issue about pertussis vaccine, some of them not yet answered, include the best product to give, the preferred method of administration, dosage required, duration of protection and the rate at which resistance declines, and the most satisfactory means by which to judge the results of immunization.

Antigens for Immunization. After much experience with preparations containing whole organisms[129a], mechanically disrupted cells[79] and toxoids[139] and with plain and alum-precipitated preparations, practice has centered in recent years on alum-precipitated triple antigens[62,71b,107] that combine diphtheria and tetanus materials with those of pertussis. The required dosage of killed whooping cough bacilli is 30 billions, given in 2 or 3 injections 1 month apart. The longer interval, in place of the weekly injections so long practiced, seems fully justified[1,115,132], as productive of better and more enduring protection. The combination of antigens gives as high-grade protection, judged by laboratory methods, as the individual elements administered separately[34a,113]. Rambar[120] has reported on a vaccine combining pertussis and parapertussis organisms.

Evaluation of Results. Three methods have been used to evaluate immunizing antigens: by testing the serum of immunized children for antibodies[34b,106b,115]; by field trial of the protection afforded a test group compared with an unimmunized control group; and by biologic assay[73] through mouse protection test. The difficulty in judging immunizing effect by the antibodies produced lies in the indefinite position antibodies have in the total protective result, and also in determining the levels deemed protective. Proof is certainly not at hand that the absence of antibodies against pertussis is indica-

tive of susceptibility. Biologic assay of pertussis antigens by mouse protection test has been required by the Public Health Service since 1948. Skin tests[4,131] are currently receiving attention. Field trial remains the most effective criterion of the value of a vaccine, evidence being sought sometimes by weight of numbers[25,61], and better, by thoroughly controlled and carefully observed smaller samples[5b,72,128,136]. American opinion favors the usefulness of preparations now used[45a], with British workers still having reservations[37,92,93]. Immunity after attack is not absolute and tends to be offset under intense and repeated exposure[42]. Immunization can be expected to do no more than an attack of the disease and hence gives no absolute immunity. Both natural and acquired resistance protect in reasonable degree, and partial protection may be expected to give a milder and a briefer clinical course.

Age at Immunization. The early age of attack and the excessive death rates in the first 6 months of life are clear indications for early immunization. The minimal protection arising from maternally acquired passive immunity theoretically favors early active immunization. Sako *et al.*[127] immunized infants aged 2 weeks to 3 months. The response as judged by antibodies formed was not equal to that at later ages but gave protection when most needed, and could be reinforced by a recall dose after 6 months. Immunization of newborn infants in the first month of life[1,34b], from 1 to 8 weeks old[152], and at 1 month[61,115] have confirmed these results and brought the impression that reactions are less severe and less frequent at these ages. Thus the age at which to start immunization depends upon epidemiological criteria. When whooping cough is prevalent or for other reasons the risk is great, consideration may be given to immunization of the mother before birth of the child or of the infant promptly after birth, in the first month. Conditions may dictate a middle position, at age 3 months, with age 6 months a desirable time under usual circumstances.

Duration of Induced Protection. Immunity after active immunization is apparently not of long duration, although adequate data by which to judge are not at hand. On the basis of agglutinins in concentration of 1:320, Miller *et al.*[108] judged a satisfactory level of protection to be present in 70% of immunized children at the end of 1 year, and in only 33% at 4 years. A working limit of 18 months for older children and 6 months to a year for infants is commonly practiced in determining the need for a booster dose, either by injection of vaccine or by agglutinogen skin test[46,47]. A third injection is commonly advised after another 2 to 3 years, or on entering school. A booster dose is indicated promptly after known exposure. Attempts to prolong protection beyond early school age are believed to be ill-advised; the danger has passed.

Serious Reactions to Immunization. Miller[106c] has brought together some 60 instances, since 1933, of death or encephalopathy after pertussis immunization. Byers and Moll[19] in a hospital experience had 15 cases of encephalopathy after pertussis immunization[38], and twice that number after the disease itself.

Chemoprophylaxis. The demonstration that streptomycin[64] brought rapid disappearance of pertussis bacilli from the respiratory tract when administered intranasally to infected infants as nasal drops or as an aerosol[9b,11] suggests the possible development of a chemoprophylaxis of whooping cough, useful with non-immune susceptibles as in meningococcus meningitis[116], or in limiting the period of communicability of

patients, as in scarlet fever[156]. Sulfadiazine has also been suggested, but with no field trial of either method.

Passive Protection. With the presently available antigens for active immunization and the demonstrated feasibility of employing them early, serums for passive protection against whooping cough have now a more limited place, aside from therapeutic use[77]. The principal indications are where epidemiological considerations make prompt protection of newborn infants[98] advisable, and for the temporary protection of older infants not immunized and subjected to the intense exposure incident to whooping cough in the family[138]. Primary active immunization after effective exposure is of no proved value.

Field trial[103] of convalescent serums, with additional confirmation by laboratory tests[112], have demonstrated 70% protection in recently exposed children, compared with controls. Children passively protected with immune rabbit serum[134] contracted whooping cough one-eighth as frequently as did children not protected.

A more adequate source of serum[45b] became available through experiments by which healthy adults with a history of whooping cough were hyperimmunized[96] with heavy doses of pertussis vaccine. The serum protected 67.9% of 308 children[94] where the expectancy of escape is about 15%, and in another series[95] 78.3% escaped infection.

Administration Control. Complete administrative control of whooping cough in a community is not possible, but an intelligent program productive of worthwhile and effective results can be developed. The inherent difficulties in control of whooping cough arise because infection is most communicable when it is least evident, and by reason of the long duration of the clinical disease and of infectiousness. Increasing use of active immunization brings a greater proportion of mild and missed cases. A single principle guides the program, mainly to center attention on the age group under 2 years. The program to follow has 4 principal parts.

The first consideration is to develop measures by which to assure vaccination of all susceptible children of preschool age. It is best accomplished through promoting the interest of practicing physicians. The need of clinics to provide service suggests faulty relations between physician and health department. Young infants living under conditions in which risk of exposure is great[2] and those living in institutions and in households with older susceptible children should have active immunization started by the time they are 1 month old, particularly when whooping cough is prevalent in the community. Other children should have immunization started by the time they are 6 months of age.

Provision is to be made for medical and nursing care for patients not attended by a physician, especially those aged less than 5 years.

A search for unrecognized and unreported cases is of value in the protection of young children from exposure and in the assurance of adequate medical care for those exposed, particularly infants. Whooping cough in patients aged less than 5 years should have precedence by public health nurses over other common communicable diseases of childhood and over all routine visits.

The fourth part of the plan is to introduce educational measures to inform the public, and particularly the parents of infants, of the danger of whooping cough and of the advantages of immunization in infancy. The idea that whooping cough is not much of a disease has little justification.

Isolation in whooping cough is ineffective. Modified isolation or separation of the patient from susceptible children and exclusion from school for 3 weeks after the first paroxysm is for the protection of susceptible children and also for the good of the patient, that he may not be exposed to other respiratory infections. Strict isolation is impracticable and is not to be insisted upon at the expense of fresh air in the open. The bacteriological control[54] of isolation through requiring two or more consecutive negative cultures is too cumbersome for practical operations.

Quarantine is limited to non-immune children, those who have not had whooping cough. Exclusion of contacts from school and public gatherings is ordinarily required for 14 days. An equally satisfactory procedure is careful observation by the school physician or nurse on arrival at school each day for 14 days after last exposure to a recognized case. Special effort is to be directed to the protection and observation of infant contacts under 2 years, and especially young infants. Passive immunization of younger non-immunized infants is practiced to advantage through administration of 20 cc. to 40 cc. of hyperimmune serum, or 5 cc. to cc. of immune rabbit serum.

Almost no progress has been made in control of the atmospheric environment where children congregate. The expense associated with ultraviolet irradiation of the air of school rooms is scarcely commensurate with the results obtained. Experiments are under way with triethylene glycol[80] in control of air in atmospheres contaminated with whooping cough bacilli.

A plea for improved reporting is rather hopeless in the face of the 18% efficiency that marks better public health practice. The value to be had from improved reporting is better opportunity for case finding; and cases can be found, 88% in the experience of Luttinger[88]. The protection of the preschool child requires that the places be known where whooping cough exists. The disease is not a primary problem of school age nor of the school physician, because more than half of the children have had whooping cough by the time they enter school.

Summary. This analysis of the epidemiology of whooping cough has brought together a noteworthy collection of anomalies in mass behavior. The initial attraction to the study was in the old observation that more girls than boys have whooping cough and that more die, this being the reverse of other common communicable diseases of childhood. The absent hand or the extra toe in anomalies of development is often only the more evident defect after an embryologic accident. A variety of other malformations are commonly found in the same person, some of little significance, and some of greater importance than the apparent disfigurement. That has been true here.

Whooping cough has a peculiar history in that it gives every evidence of an old established disease, and yet came to the attention of physicians centuries after the other diseases of the group had been described. It lacks the long and honorable pedigree of mumps.

Pertussis presents the clinical anomaly of a disease which is unrecognizable when it is an active acute infection and becomes a real disease only when that stage is past, when temperature is normal and the patient is not so much sick as afflicted.

Pathological changes are neither deep-seated nor general (the primary infection attacks superficial mucous membranes), and yet deaths are frequent and resistance to second attack

is long continued. The newborn infant has little or none of the maternally transferred passive protection so characteristic of the other specific infections of childhood. Deaths from whooping cough in the first year of life are inordinately frequent, representing some 70% of all deaths from this disease, and more than for all other common communicable diseases of childhood combined.

As a mass disease of populations, the striking epidemiologic characteristic is the reversed sex ratio, but there are others. The pronounced seasonal swing and the summer decline so characteristic of respiratory diseases are not a feature of whooping cough. The higher death rate is in the south rather than the north, again the reverse of such other respiratory infections as scarlet fever, diphtheria and measles. Whooping cough was the first disease of childhood to demonstrate a preponderance of rural incidence over urban. Pertussis gives evidence of being the most widely diffused of all communicable diseases of childhood, as evidenced by the experience of recruits in military service. And the list of peculiarities is not ended.

Whooping cough is an important disease despite its classification with the minor infections and the light regard in which it is held. The disease warrants the attention demanded by the number of deaths it causes.

Emphasis has been made in another place of the value of the unusual circumstance, as distinguished from the ordinary and routine, in solving epidemiologic riddles. Whooping cough has more than its share of unusual circumstances, of anomalies in behavior, and hence has a special appeal to epidemiologists in the search for a clearer definition of principles that govern mass disease.

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BOOK REVIEWS AND NOTICES

PROCEEDINGS OF THE SECOND CLINICAL ACTH CONFERENCE. Edited by JOHN R. MOTE. Vol. I, Research: pp. 531, 276 ills.; Vol. II, Therapeutics: pp. 716, 311 ills. Philadelphia: Blakiston Co., 1951. Price, $8.50 per volume.

THESE 2 volumes contain 102 papers which were presented at the second clinical ACTH conference held in Chicago on December 8 and 9, 1950. Volume I consists of articles dealing with research on the more fundamental aspects of ACTH and adrenal cortical function. Sections are devoted to general adrenal cortical physiology and adrenal cortical steroid secretion and excretion; the kidney and electrolytes; nitrogen metabolism; carbohydrate and fat metabolism; Vitamin metabolism; the adrenal gland and the hemopoietic system; and the action of ACTH and cortisone on the acute inflammatory response.

The second volume relates primarily to the effects of ACTH and cortisone in the treatment of disease syndromes. Among the conditions discussed are rheumatoid arthritis, gout, rheumatic fever, acute disseminated lupus erythematosus, periarteritis nodosa, bronchial asthma, spontaneous hypoglycemia, ulcerative colitis, burns, certain blood dyscrasias, and several varieties of neoplasm. Some of the reports either confirm or extend previous studies, while others introduce new possibilities for ACTH and cortisone in Chagas' disease, black-widow spider bite, and copperhead snake bite. In addition, there are reported experiences with the use of intravenous as well as long-acting preparations of ACTH.

A very valuable feature is the inclusion of the highly informative discussions which followed the presentation of each paper. This report, like its predecessor, should prove helpful both to the clinician and the research worker. C. Z.

THE 1950 YEAR BOOK OF GENERAL SURGERY. By EVARTS A. GRAHAM, A.B., M.D., Prof. of Surg., Washington Univ. Sch. of Med.; Surgeon-in-Chief, Barnes Hosp., and of Children's Hosp., St. Louis, with a section on ANESTHESIA by STUART C. CULLEN, M.D., Prof. of Surg. and Chairman, Div. of Anesthesiol., State Univ. of Iowa Coll. of Med. and Hospitals. Pp. 670; 193 ills. Chicago: Year Book Publishers, Inc., 1950.

THIS volume maintains the high standards of reporting and review for which the Year Book of General Surgery has previously earned high regard. The section dealing with thoracic surgery appears to have received special attention.

The review of surgical progress in the past decade is interesting. This reviewer does not agree entirely with the contributions which the editor has included as being the most important. Moreover, the failure to mention the alarm response seems likely to prove a definite omission in the years to come.

This book offers as its greatest value a considered, selective review of the surgical and pertinent medical literature for the past year. J. H.

BRAIN METABOLISM AND CEREBRAL DISORDERS. By HAROLD E. HIMWICH, M.D., Chief Clin. Res. Branch, Med. Div., Army Chemical Center, Md. Pp. 451; 52 ills. Baltimore: Williams & Wilkins, 1951. Price, $6.00.

To the Reviewer this book was a pleasant experience and surprise. It is well written and the arrangement is orderly so that reading it is not difficult. If the reader wishes to avoid the involved technical part, he can do so without losing the trend of thought. The bibliography of 1042 references, which are not readily available elsewhere, make the book of value if for no other reason. In this Reviewer's opinion, it should be in every physician's library, and it is a must for the neurologist, psychiatrist, neuropathologist, neuroanatomist, and neurosurgeon. S. G.

VITAMINS AND HORMONES. Vol. 8. Edited by ROBERT S. HARRIS, Prof. of Biochem. of Nutrition, Mass. Inst. of Technol., and KENNETH V. THIMANN, Prof. of Physiol., Harvard Univ. Pp. 342; 23 ills. New York: Academic Press, Inc., 1950. Price, $6.80.

THE editors have again assembled outstanding investigators from this country and abroad to prepare chapters of current interest. Condensed and yet thoroughly reviewed, subjects include Vitamin B_{12} (Zucker and

Zucker), Pyridoxine and Fat Metabolism (Sherman), Antistiffness Factor (von Wagtendonk and Wulzen), Metabolism in Neurospora (Mitchell), Physiology of Relaxin (Hisaw and Zarrow), Estrogens and Progestrone (Courrier), Posterior Pituitary Hormones (Stehle), and Steroid Configuration (Shoppee). The concise and interesting presentation of each subject should have wide appeal. H. S.

NEW EDITIONS

A Text-Book of X-Ray Diagnosis. Vol. 1. By British Authors. Edited by S. Cochrane Shanks, M.D., F.R.C.P., F.F.R., Director, X-Ray Diag. Dept., Univ. Coll. Hosp., London, and Peter Kerley, M.D., F.R.C.P., F.F.R., D.M.R.E., Director, X-Ray Dept., Westminster Hosp., Radiol., Royal Chest Hosp., London. 2nd ed. Pp. 434; 439 ills. Phila.: W. B. Saunders Co., 1950. Price, $12.00.

The 2nd edition of this series of books on Roentgen-ray Diagnosis by British Authors has been arranged in 4 volumes: Head and Neck, Abdomen, Chest, and Bones and Joints.

Volume I covers the Central Nervous System, Teeth and Jaws, the Eye, the Accessory Sinuses, and the Temporal Bone. Chapters on Ventriculography and Encephalography and Cerebral Angiography are included under the Central Nervous System.

As in the 1st edition, the reproductions are negatives (with the exception of those of the teeth and jaws).

The material is covered in concise and comprehensive fashion. Reading is easy and the work maintains its reputation as an excellent reference. The sections on radiographic technique are well illustrated. H. W.

The Diagnosis and Treatment of Adrenal Insufficiency. By George W. Thorn, M.D., Hersey Prof. of the Theory and Practice of Physic, Harvard Med. Sch. 2nd ed. Pp. 180; 35 ills. Springfield, Illinois: Charles C Thomas, 1951. Price, $5.50.

This brief, authoritative text provides an excellent reference for the details of the diagnostic study and careful management of patients with any of the forms of adrenal cortical hypofunction. The principal change in the present edition is the substitution of a chapter dealing with the use of synthetic cortisone acetate for a comparable chapter on compound A in the 1st edition. A few additions are made in the sections on basic adrenal physiology and biochemistry, while the clinical portion of the book is unaltered. C. S.

Immunology. By Noble Pierce Sherwood, Ph.D., M.D., F.A.C.P., Prof. of Bacteriol., Univ. of Kansas, Pathol. to Lawrence Memorial Hosp. 3rd ed. Pp. 731; 15 ills., 7 color plates. St. Louis: C. V. Mosby Co., 1951. Price, $8.00.

This is the first revision in 10 years of a well-known text by a leading immunologist. It is intended for the use of the medical student and the undergraduate bacteriology major. Since the material is presented in clear language from the point of view of the student, it is a pleasure to read.

The author might well have used the title "Applied Immunology" because the emphasis is not upon fundamental mechanisms or theoretical considerations but upon the application of immunologic phenomena to medical practice. The various subjects are discussed in relation to therapy and prophylaxis rather than as separate entities. An example is the section on "Wound Infections". Indeed, the author has not confined himself to immunology except within a broad interpretation. The emphasis upon practical immunology is striking, one entire chapter being devoted to the importance of antibodies in diagnosis. The reviewer does not intend these remarks as an expression of disappointment. On the contrary, he finds the approach used here refreshing and a distinct relief from the formal treatment which characterizes the usual textbook of immunology.

One unfavorable criticism which must be made is the author's practice of developing his subjects by a succession of literature citations. Although the choice of quoted work is in the main excellent, the net effect is interruption of the train of thought. Had the material been digested and presented as a critical review, the result would have been a smoother presentation. The subject of the origin of antibody is one which suffers from this type of approach. In addition, the arrangement is sometimes haphazard, as, for example, the inclusion of the interference phenomenon in an irrelevant chapter.

The best feature of this text is the list of references at the end of each chapter. These are particularly well chosen and up-to-date. The index has been carefully prepared, although cortisone is omitted, despite its inclusion within the text. The illustrations, largely drawings, are pertinent and well done. This text should be valuable to the medical student to whom sufficient time is available for a separate course in immunology. To the practicing physician, it can be recommended as a good reference book in immunology, not because it is comprehensive or authoritative, but because most topics which come to one's mind are dealt with briefly and accompanied by well chosen references. E. S.

Clinical Heart Disease. By Samuel A. Levine, Harvard Med. Sch., 4th ed. Pp. 556; 192 ills. Phila.: W. B. Saunders Co., 1951. Price, $7.75.

The chief virtues of this book have been its clarity and its practicality. These virtues are retained in this 4th edition. Moreover, the section on electrocardiography has been completely revised with the aid of Dr. Harold D. Levine. Electrocardiography is treated not as an end unto itself, but as another tool in the clinical appraisal of the patient. W. S.

NEW BOOKS

Medical Progress in 1951 and Cumulative Supplement of British Encyclopaedia of Medical Practice. 1951. 2 vols. Edited by Rt. Hon. Lord Horder, G.C.V.D., M.D., B.Sc., F.R.C.P., Physician to the King, Consulting Physician to St. Bartholomew's Hospital. London and Toronto: Butterworth & Co., Ltd., 1951. Price, $14.00.

The Medical Progress volume is written in 3 parts. Part I, entitled "Critical Surveys," is a factual presentation of the recent advances in the various fields of medicine. Part II consists of "Recent Developments in Pharmacology and Therapeutics". This section seems to have suffered to make room for the lengthy Part III. The bulk of the volume is contained in Part III entitled "Abstracts". This section contains an unusually adequate list of abstracts of articles of general medical and surgical interest. They are arranged to conform with subject headings in the British Encyclopaedia of Medical Practice.

These books are well indexed and contain easy to read, concise reviews of current medical advances and problems. Their coverage is so broad and general that they will be of interest to physicians in all spheres of medicine. Their strongest appeal will be to busy practitioners as a reference volume.

H. B.

Vitamin E: Annotated Bibliography 1940 to 1950. Compiled by Philip L. Harris and Walma Kujawski, Research Labs. of Distillation Products Industries. Pp. 184. New York: The National Vitamin Foundation, Inc. Price, $3.00.

This work reviews briefly over 1500 scientific publications and patents pertaining to vitamin E. The annotations are grouped in sections with emphasis on physiologic, chemical, and medical aspects. The compilation should be a helpful guide to the pertinent literature concerning practically any phase of interest in this important vitamin.

C. Z.

The Growth, Replacement, and Types of Hair. By J. B. Hamilton, A. E. Light, and Others. Pp. 290; ills. New York: New York Academy of Sciences. 1951. Price, $4.00.

Heart Disease in Pregnancy. By A. Morgan Jones, M.Sc., M.B. (Vict.), F.R.C.P. (London). Pp. 57; 6 ills. New York: Grune & Stratton, Inc., 1951. Price, $1.50.

Cancer as I See It. By Henry W. Abelmann, M.D., Pp. 100. New York: Philosophical Library, 1951. Price, $2.75.

Fever Therapy. By H. Worley Kendell, M.D., F.A.C.P., Prof., Physical Med., Univ. of Illinois Research & Educat. Hosp., Chicago. Amer. Lecture Ser., No. 80. Pp. 101; 15 ills. Springfield, Ill.: Charles C Thomas, 1951. Price, $2.25.

How to Stop Smoking. By Herbert Brean. Pp. 96. New York: Vanguard Press, Inc., 1951. Price, $1.50.

Papain. By M. L. Tainter, C. E. Alford, A. Arnold, H. Blumberg, O. H. Buchannan, *et al.* Pp. 296; 32 ills. New York: New York Academy of Sciences, 1951. Price, $3.00.

The Doctor. His Career, His Business, His Human Relations. By Stanley R. Truman, M.D. Pp. 151. Baltimore: Williams & Wilkins Co., 1951. Price, $3.00.

Here's to Sobriety. By Thomas Fullam. Pp. 208. New York: Abelard Press, Inc., 1950. Price, $2.50.

Parasitic Infections in Man. Symposium No. 4. Held at the New York Academy of Medicine. Pp. 229. New York: Columbia University Press, 1951. Price, $4.50.

A Classified Bibliography of Gerontology. By Nathan W. Shock, Chief, Sect. on Gerontol., Natl. Heart Instit., Natl. Institutes of Health, and Baltimore City Hospitals. Pp. 599. Stanford Univ., California: Stanford Univ. Press, 1951. Price, $15.00.

Emotional Factors in Cardiovascular Disease. By Edward Weiss, M.D., Prof., Clin. Med., Temple Univ. Sch. of Med. Pp. 84. Springfield, Ill.: Charles C Thomas, 1951. Price, $2.25.

Leprosy. Edited by Roy W. Miner. Pp. 142; 52 ills. New York: New York Academy of Sciences, 1951. Price, $2.75.

This series of 15 papers is the result of a Conference on Leprosy, held by the Section of Biology of the New York Academy of Sciences, Nov. 10 and 11, 1950. A broad up-to-date view of the most important aspects of the disease is provided by competent authorities in their respective fields. Included are a general history of leprosy in the United States and discussions on the epidemiology, sociology, and control of the disease. Excellent summaries of the bacteriology and of the pathology and pathogenesis of leprosy are given. Methods for laboratory diagnosis are evaluated and the cutaneous and ocular manifestations are discussed. Experimental and clinical experiences in the treatment of leprosy are given with emphasis on recent chemotherapeutic advances.

C. Z.